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PRELIMINARY REPORT ON A

NEW LOCAL ANESTHETIC (NUPERCAIN)*

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NUPERCAIN is a new local anesthetic that has been used (under the name of percain) in Europe and praised because the resulting anesthesia persists for six or eight hours.

Miescher[1] of Basle, working with the quinine nucleus, has synthesized this new substance which is alpha-butyloxycinchonic acid diethyl-ethylen-diamide hydrochloride.

Physical Properties: Nupercain is in the form of colorless crystals, is neutral in reaction, readily soluble in water and may be repeatedly boiled. If a solution is rendered alkaline, the drug precipitates as a free base; hence it must be used in a slightly acid solution and kept in alkaline free containers. The drug, as we have used it, is actually dispensed in ampules dissolved in physiological saline solution acidified by one drop of concentrated hydrochloric acid per liter of solution.†

Toxicity: Uhlman[1] has studied the drug pharmacologically and reports it five times as toxic as cocaine when injected subcutaneously into rabbits and guinea pigs; Lipschitz and Laubender[2] find it twice as toxic as cocaine when injected intravenously into rabbits; and Gray,[3] using it subcutaneously in dogs, finds it twice as toxic as cocaine. Uhlman also reports that the greater the concentration the greater the toxicity. Freund[4] has reported 1 death following subcutaneous injection of 130 c.c. of 1:1000 solution. Heckenbach[5] has reported 1 death following a paravertebral anesthesia. The post-mortem examination confirmed the presumption that the injection had been made inadvertently into the spinal canal where the prick of the needle was distinctly visible. Siebner[10] reports the death of a patient with hyperthyroid disease after the injection of 90 c.c. of 1:1000 solution. The death was not attributed to nupercain but he has reduced the amount used in later thyroidectomies.

Patients recovered from 750 and 1500 mg. given inadvertently. The former was not sick; the latter was severely poisoned.

The following unpublished deaths are a warning of the toxicity of nupercain:

1. Cesarian section. Three hundred and eighty milligrams of nupercain in 1:1000 solution injected subcutaneously. Twenty minutes after injection, vomiting, convulsions, cyanosis, tachycardia, death. Autopsy revealed severe pyelonephritis with abscesses in right kidney. Death was ascribed to the renal condition.

2. Through mistake a 1 per cent solution was used instead of 1:2000. Total dose not stated. Death resulted, autopsy revealing hyperthyroidism and status lymphaticus.

3. Through mistake a 10 per cent solution was injected. Death occurred ten minutes after an unstated dose.

4. Eighty cubic centimeters of 1 per cent

† It is readily adsorbed by filter paper. Therefore if filtered the first 10 per cent of the filtrate must be discarded.

* Read before the Section of Genito-Urinary Surgery, New York Academy of Medicine, February 19, 1930.

solution (800 mg.) was injected by mistake. Death was almost immediate.

5. An unstated amount of 1 per cent solution was injected into the bladder. Death occurred in ten minutes.

This toxicity is compensated for by the fact that nupercain is 10 times as anesthetic as cocaine, may be used in a very diluted solution and produces a more enduring anesthesia.

Clinical Reports: Christ,[6] Hofer,[7] Ritter[8] and Von Seeman[9] reporting 500, 300, 309 and 400 cases of infiltration anesthesia respectively, have all reached the same conclusions as regards non-irritability locally, absence of susceptibility and prolonged anesthesia lasting an average of six to eight hours. Christ reports that one-fifth of his cases did not have postoperative pain. Local vascular dilatation is like that of procaine and controllable with adrenalin (10 drops to each 100 c.c. of solution).

Christ prefers 1:1000 solution of nupercain (the other three 1:2000) to which is added 5 drops of dilute hydrochloric acid per liter and recommends as maximum doses for local infiltration, 400 c.c. of 1:2000 solution, 150 c.c. of 1:1000 solution or 50 c.c. of 1:500 solution.

Heckenbach[5] used as his maximum dose 400 c.c. of 1:2000 solution, Von Seeman[9] 350 c.c. of 1:2000 or 200 c.c. of 1:1000 and Siebner[10] 200 c.c. of 1:1000 with an additional 100 c.c. of 1:2000.

Spinal anesthesia has been reported by Ziegner[11] on 52 cases. He uses a 1 per cent solution, finds 10 mg. too much and is now using 8 mg. No permanent injuries were noted. The duration of the anesthesia is from three to ten hours. Christ[6] used 4 c.c. of 1:1000 solution in a few cases.

Caudal anesthesia with 30 c.c. of 1:500 solution has been recommended by Heckenbach.[5]

Mucous membrane (urethra and bladder) anesthesia has been entirely satisfactory, especially long persisting and without accident in 1:1000 solution to which is added 10 to 15 drops of adrenalin (1000 cases as reported by Heckenbach[5]). Siebner[10] also recommends 1:1000 solution. (Uhlman[1] reports nupercain ten times more anesthetic than cocaine on the rabbit's cornea.)

PERSONAL EXPERIENCE

This paper is founded on the use of nupercain for caudal (59 cases), spinal (46 cases), local and surface (urethral) anesthesia. In no instance has adrenalin been added to the solution.

CAUDAL ANESTHESIA

Thirty cubic centimeters of a 1:1000 solution of nupercain are injected into the sacral canal.*

This anesthesia has been employed 59 times, 40 times in the office for cystoscopic fulguration of bladder tumors or ulcers (11 cases), observation and pyelogram (13 cases), tuberculosis of bladder (2 cases), urethral caruncle (2 cases), litholapaxy (oxalate stone 2.5 cm. in diameter), urethroscopic treatments (9 cases) and curetting perineal urinary sinus (2 cases); in the hospital for observation and pyelogram (12 cases), cystoscopic fulguration of bladder tumors (1 case), fulguration of bladder ulcer (2 cases), tuberculosis of bladder (1 case), punch operation (1 case), dilatation of urethral stricture (1 case) and removal of perineal packing (1 case).

Anesthesia has been satisfactory except in 5 cases (3 of these were given by the hospital interns, the only ones they gave).

Two patients had previously exhibited a susceptibility to procaine.

Case 1. Male, fifty-six years old. Office cystoscopic treatments for bladder tumor six times during 1928. The patient was on digitalis, an extra dose of which he took before each treatment. Extremely apprehensive. Caudal anesthesia by 30 c.c. of 2 per cent procaine each time. Before the whole dose had been given he would always complain of palpitation, dizziness and tinnitus which increased for from five to ten minutes, the pulse becoming irregular and rapid (140–150).

* Twice 35 c.c. of 1:1000 solution and twice 25 c.c. of 1:2000 solution were used.

On November 12, 1929, cystoscopic examination under nupercain caudal anesthesia. No reaction subjectively or objectively. No tumor seen.

Case II. Male, fifty-five years old. Office cystoscopic treatments for bladder tumor under procaine caudal anesthesia (30 c.c. of 2 per cent solution); eight in 1927–28–29. On October 21, 1929, nupercain caudal anesthesia was given but the patient was not informed of the change as it was suspected that the reaction was partly psychic. The following note was made: "He has had eight caudal anesthesias of procaine (30 c.c. of a 2 per cent solution). Each time he had a reaction which occurred after the first 5 to 10 c.c. had been injected. There would be mild delirium; he might not recall what had happened. However, little change was noted in the pulse rate or blood pressure during this period, so the whole amount was injected. He would be clear mentally in from ten to fifteen minutes. Today caudal anesthesia of nupercain was injected quickly and there was no reaction. Tumor fulgurated."

Caudal anesthesia under nupercain was repeated December 4, 1929. No reaction and no tumor seen.

One case seems to have shown personal susceptibility to nupercain.

Case III. Male, fifty-seven years old. During 1928–29 he was given thirteen caudal anesthetics of 30 c.c. of 2 per cent procaine for cystoscopic fulguration of bladder and urethral tumors. He had slight dizziness and a congested feeling in the nose each time. On November 20, 1929, he was given a caudal anesthesia of nupercain (30 c.c. of 1:1000 solution) and was informed of the change. He had the same symptoms as with procaine except that the dizziness was more intense and prolonged. He prefers procaine.

The onset of anesthesia is said to be somewhat delayed as compared to procaine. Thus a dentist to whom we gave some nupercain found that anesthesia of a tooth might be delayed as long as thirty minutes, which was interpreted as slow conduction through bone. We have not noted this delay.

Duration of the anesthesia, as determined from the patient's first discomfort, e.g., burning on urination, etc., occurred in from one to eight hours after injection, an average of five hours (30 cases). One excellent anesthesia was the litholapaxy, which was done in the office, upon a patient who was suffering from incontinence of urine due to imperative urination. The procedure was painless. He returned to the office eight hours later, having slept most of the afternoon, and passed 5 oz. of urine without discomfort. Next morning his urine was free from blood. He remained well.

Five patients had no pain whatever following cystoscopy. Two had pain when a meatotomy was performed although simultaneous cystoscopy was painless. Fulguration of an ulcer was painless except when the bladder was distended to over 120 c.c. (This ulcer was later resected under nupercain spinal anesthesia. No pain was felt during abdominal section but the bladder sensibility to distension remained so acute that ether had to be used.)

The one disadvantage to using nupercain caudal anesthesia in the office is the temporary paralysis that may ensue. Twice this delayed the patient's departure.

Case IV. Male, thirty-one years old, using crutches because of almost complete paralysis (infantile) of the leg muscles. On November 8, 1929, under nupercain caudal anesthesia (30 c.c. of 1:1000 solution) he was urethroscoped for diagnosis. The anesthesia was perfect. On account of the paralysis of the legs he was carried from the table to a couch, but was able to leave in two and one-half hours.

Case V. Male, thirty-seven years old. On December 2, 1929, under nupercain caudal anesthesia (30 c.c. of 1:1000) a pyelogram was made. This patient had to be assisted from the table and was delayed in the office two and one-half hours.

The possibility of retention of urine following caudal anesthesia with nupercain should be borne in mind. One patient passed air twenty hours after the anesthesia, which means he had some retention during that time.

SPINAL ANESTHESIA

Spinal anesthesia has been employed in 46 cases. Ten grains of veronal* were given the night before and repeated one hour before the operation. Fifty milligrams of ephedrine sulphate were given orally when the patient left the bed for the operating room. Ampules of procaine containing ephedrine sulphate (50 milligrams) were used to anesthetize the interspace. Thus the patient received in all 100 milligrams of ephedrine.

The injection may be made in the sitting position provided the patient lies down immediately thereafter.

The solution employed by us at first was 1:1000. As no toxic symptoms ensued, we have gradually increased the concentration in successive cases† and are now injecting 2 c.c. of a 1:200 solution. No intoxication or paralysis has been observed. There has been one spinal headache.

The height to which the anesthesia reaches depends on the interspace used, the degree of dilution with spinal fluid, the amount of anesthetic injected and the amount of spinal fluid withdrawn.

There were 24 suprapubic bladder operations: prostatectomies (9 cases‡), prevesical section and bilateral ligation of the vasa deferentia (11 cases), fulguration of bladder tumor (2 cases), resection of bladder ulcer (1 case), closure of fistula (1 case).

There were 9 kidney operations: 2 pyelotomies for stone (one a very bad risk, the other including a division of ureteral stricture), 1 heminephrectomy for a supernumerary ureter which opened into the urethra; 3 nephrectomies, 1 exploration of the loin (disclosing perisplenic suppuration and absence of kidney), 1 perinephritic abscess and 1 nephropexy.

A patient with renal colic following a cystoscopic examination elsewhere was given a spinal injection of 5 c.c. of 1:1000 solution. The pain stopped in five minutes but returned in two hours; a second patient with renal colic was given 1 c.c. of 1:200 and this was ineffective. (Attention is called to spinal anesthesia as a method of relieving renal colic.)

There were 11 urethral and intravesical operations: external urethrotomy (2 cases 1 with extensive periurethral gangrene), litholapaxy (2 cases), fulguration of bladder tumor (2 cases), "punch" operation (4 cases), resection of a tuberculous perineal sinus (1 case).

The anesthetic was perfect 36 times (2 patients towards the end of the operation complained of a dull ache but no supplemental anesthetic was necessary). Three (2 renal and 1 vesical) were given ether on complaint of pushing or pulling sensation. Seven were given supplementary anesthesia for pain. One of these patients, after the bladder had been exposed suprapubically, complained of pain when the bladder was distended. Another (this was the second case in which nupercain was used) had only parasthesia of his legs so he was given a spinal injection of procaine crystals (120 mg.) which gave perfect anesthesia. A third patient had a large bladder tumor removed and the base fulgurated and the bladder closed about a drainage tube; then the peritoneum was opened for prognostic purpose and, as the peritoneum was sensitive, ether was given. The fourth was the patient having perisplenitis. She had pain as the diaphragm was pulled upon. The fifth and six, both kidney cases, required nupercain 1:1000 in the upper angle of the wound. The seventh, a prostatectomy, had anesthesia only of the legs due to faulty technic.*

*Recently we have employed scopolamine (grains $\frac{1}{200}$) and morphine (grain $\frac{1}{4}$) preliminary anesthesia and have eliminated one of the 50 mg. ephedrin doses.

† Six patients received 5 c.c. of 1:1000 solution, 4 received 2.5 c.c. of 1:500, 6 received 1.5 to 2.75 c.c. of 1:250, 2 received 1.5 c.c. of 1:200 and the others received 2 c.c. of 1:200.

‡ One plus diathermy for tumor of bladder; one plus diverticulectomy.

*One of us (K) has noted that since he no longer uses novocaine, a chronic eczema of the fingers of five years' duration has disappeared.

We have further learned that for mucous membrane anesthesia, a 1:250 solution is more effective than any local anesthesia, we have previously employed.

Recently we have twice repeated spinal injection because the anesthesia was inadequate.

During the operation there were no alarming symptoms. Variations in pulse and respirations could readily be attributed to the operation. Vomiting during the operation did not occur. (Only 3 patients vomited thereafter, one of them but once.)

The systolic blood pressure of 29 patients fell an average of 18 points; that of 11 others did not fall. The maximum fall was 70 points.

The duration of the anesthesia varied from one and a half to twelve hours.

The average duration was between seven and eight hours. Nine patients did not complain of any postoperative pain, but all open operations required sedatives the following night.

One patient (prevesical section and ligation of the vasa deferentia) had a slight ache in the wound during the operation. This persisted and required codeine seven hours later.

Case VI. One patient, a man seventy-three years old, had a cystotomy for drainage and removal of a large phosphatic stone from a diverticulum ten days previously. He was given 11 mg. of nupercain in a 1:250 solution. Two large diverticula of the bladder were removed in two and one-half hours. Two hours and forty minutes after the spinal anesthesia had been given, a very large adenomatous prostate was removed without pain. The patient was in poor condition and lost much blood. He was given a blood transfusion before he was returned to his bed. He felt no pain and made an uneventful recovery.

Case VII. A woman, fifty-six years old, for years had suffered from symptoms characteristic of ulcer of the duodenum. Her gastrointestinal *x*-ray series showed a defect characteristic of ulcer. She developed a fever with pain and rigidity in the left loin, quite high up. She was given a spinal anesthetic of nupercain and cystoscoped. The right kidney seemed to be functioning normally; the left ureteral orifice could not be found even with the aid of indigo carmine. She was accordingly removed to the operating room and one hour and forty minutes after anesthetization, the left loin was opened and explored. A kidney could not be found but when the exploration was extended up under the diaphragm, the peritoneum was opened, the spleen found small and adherent and further investigation revealed a retroperitoneal caking of the fat behind and beyond the spleen. Manipulation at this point (about two hours after anesthetization) was painful, so general anesthesia was given while the infiltrated area was explored to a depth of about 5 cm. No gross suppuration was disclosed. There was considerable venous oozing and the distance from the superficial wound to the point of exploration was so great that it seemed wise to discontinue the search. The oozing point was packed, general anesthesia discontinued. The suturing excited no pain. The sensitiveness in this case was interpreted as being a technical defect in that the anesthesia had not been carried high enough. Indeed had the exploration extended no further than the kidney, the anesthesia would doubtless have been entirely successful. Operation was completed with the patient awake and not complaining of pain. Recovery uneventful. Symptoms relieved.

A STUDY OF THE FALL IN BLOOD PRESSURE FOLLOWING SPINAL ANESTHESIA

For the past three years we have kept a record of the blood pressures of patients who submitted to spinal anesthesia. The technic has been the following:

The patient's blood pressure is taken. Ephedrine is then administered and the blood pressure taken again. The spinal anesthetic is then given and thereafter the blood pressure is taken every five minutes for thirty minutes, then every fifteen minutes until the pressure begins to return definitely toward normal, if it has not already done so during the half hour.

During these years we have employed three anesthetics; first procaine crystals (usually 120 mg.), then the mixture called spinocaine (usually 200 mg. of procaine) and finally nupercain. We have thus obtained quite complete blood pressure records on 43 procaine spinal anesthesias, 54 spinocaine anesthesias and 41 nupercain anesthesias.

A detailed statistical study of the blood pressure readings would have little value, for these are influenced by a number of imponderable factors such as arteriosclerosis, operative shock, loss of blood and most of all the patient's apprehension. Thus 10 patients were twice given spinal anesthesia with the same solution and as far as possible under the same conditions. The second anesthesia was no more disturbing than the first, but the blood pressure curves never matched any more closely than might those of 2 unrelated patients.

Yet every effort was made to make the technic comparable. One hundred milligrams of ephedrine were administered before operation when procaine or nupercain was used; 50 mg. when spinocaine was used. During operation the patient's head and shoulders were lowered about 15° below the hips. In order to lessen the patient's emotional reaction, morphine or veronal was employed. We cannot say that one of these was more effective than the other.

But in view of the dissimilarity in chemical composition between procaine and nupercain, it has seemed worthwhile to attempt a comparison of the blood pressure curves with reference to 2 points: (1), the total fall in blood pressure, and (2) the curve of blood pressure.

The average maximum fall of blood pressure after procaine was 31 mm., after spinocaine (perhaps because less ephedrine was used) 39 mm., after nupercain 18 mm. For a few patients the vasoconstrictor effect of the ephedrine was never overcome by the vasodilatation of the spinal anesthesia. Such patients had at all times after the ephedrine was administered a blood pressure higher than before. Our nupercaine series shows 11 such cases (25 per cent), the procaine series 4 (9 per cent), the spinocaine series 3 (6 per cent).

There is a marked difference in the curve of blood pressures after nupercain as compared with procaine and spinocaine. When the blood pressure drops little if at all, this distinction does not appear. When the whole series is plotted the nupercain series shows almost a straight line, the 2 procaine series a gradual decline with its lowest point at the end of the half hour. But in individual cases the difference in the curve shows clearly and may be depicted by a curve of those cases that were the least influenced by ephedrine. We have arbitrarily chosen a drop in blood pressure of at least 20 mm. or more as representative.

Eleven nupercain cases dropped 20 points or more. The drop was almost immediate, within the first five minutes. The lowest point was reached in twenty-five minutes and between thirty and forty-five minutes after the spinal injection had been given the blood pressure had returned to where it stood five minutes after the anesthetic had been injected. The subjoined table shows the fall of blood pressure measured in millimeters of mercury at five-minute intervals after nupercain (11 cases), procaine (23 cases) and spinocaine (27 cases).

Minutes	5	10	15	20	25	30	45
Nupercain	19	20	23	23	29	22	17
Procaine	7	7	21	20	31	31	17
Spinocaine	9	15	24	29	31	38	27

It has been extremely reassuring to find that the blood pressure begins to return to normal as soon after nupercain as it does after procaine and to be reassured that an initial sharp drop in blood pressure after nupercain does not usually imply a further drop of 30 to 50 points as would be the case after procaine.

LOCAL ANESTHESIA

Local anesthesia (1:1000 solution) was employed in a few cases, cystotomy, circumcision, urethral caruncle, meatotomy and incision of abscess. It was efficient.

One of us has had 3 teeth extracted under nupercain (1:1000 solution) anesthesia. The anesthesia was perfect. Twelve hours later on retiring there was no pain. The next morning one side was sore but on the other side there never was pain.

A patient with bilateral hydrocele was anesthetized with procaine on the right side, with nupercain on the left. The right side was sore ninety minutes later; the left side did not become sore.

The maximum dose used by us was 60 c.c. of 1:1000 solution.

SURFACE (URETHRAL) ANESTHESIA

Five cubic centimeters of a 1:500 solution is injected into the anterior urethra and held in for three minutes. Then an additional 10 to 15 c.c. are gently forced into the posterior urethra and bladder. This has been entirely satisfactory for the gentle passage of instruments through a sensitive urethra. A 1:200 solution in 1 case controlled the pain of a chancroid of the glans and prepuce.

CONCLUSIONS

1. Nupercain, in about ten times the dilution of cocaine, is an excellent local anesthetic.

2. The solution must be kept slightly acid.

3. It may be boiled. It may be used in conjunction with adrenalin or with procaine.

4. The minimal reported lethal dose for an adult human being is 90 mg. (90 c.c. of 1:1000 solution). Individuals have survived the administration of 750 and 1500 mg.

5. Several surgeons have recognized 200 c.c. of a 1:1000 solution as the maximum dose for local anesthesia. Our maximum dose has been 60 c.c.

6. We have usually given 30 c.c. of 1:1000 solution (30 mg.) for caudal anesthesia; 2 c.c. of 1:200 solution (10 mg.) for spinal anesthesia.

7. The failure of block anesthesia, whether caudal or spinal, may be attributed to an error of technic.

8. Nupercain is preferable to procaine for,

(a) Personal susceptibility to nupercain is negligible as compared to procaine, and

(b) The resultant anesthesia always lasts ninety minutes, and usually as long as six to eight hours.

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DISCUSSION

Dr. Jeck: I shall base my discussion on the following four methods of anesthesia in which we have employed nupercain:

1. Locally in the urethra.
2. As a caudal or epidural anesthetic.
3. As a local infiltration anesthetic.
4. As a spinal anesthetic.

1. For the past two months I have used nupercain locally in the urethra to a considerable extent. In general I have found it quite as satisfactory as the 10 per cent novocaine solution which I had previously employed. I have never seen any constitutional symptoms as a result of its use in this way.

2. Dr. McLellan has given for me a number of caudal or epidural nupercain anesthesias to alleviate the pain of cystoscopic examination and treatment. In each instance he used 30 c.c. of a 1:1000 solution. The anesthesia was very satisfactory in all cases. He recently anesthetized a patient of mine who is a doctor. The latter had a small papilloma in the vertex of his bladder and was extremely sensitive to cystoscopic manipulation. I burned the papilloma with the high frequency current, the entire job taking some thirty minutes. The doctor did not evince the slightest discomfort at any time during the procedure.

I think there is no doubt that the effects of nupercain as an epidural anesthetic are much more lasting than the effects of novocaine. I can recall several instances where I had given novocaine (30 c.c. of a 2 per cent solution) as a caudal anesthetic and while the anesthetic was perfect for fifteen or twenty minutes, after that time it wore off to such an extent that further cystoscopic manipulation was done with considerable difficulty and much discomfort to the patient.

3. I can relate only one personal experience with nupercain employed as a local infiltration anesthetic and that was in an operation for bilateral hydrocele. The operation was per-

formed on the Urological Service at Bellevue. Both hydroceles were quite large. On the right side I employed 25 c.c. of 1:1000 nupercain solution. On the left side 30 c.c. of ½ per cent solution of novocain were employed. While the right side was actually somewhat larger than the left, less of the nupercain solution was used than the novocaine which, however, was probably due only to the fact that our supply of nupercain was limited.

The anesthesia was very satisfactory on both sides. However, the patient did complain a little less on the suturing of the skin of the right side than he did when the same procedure was carried out on the left. Certainly in this one instance the nupercain worked every bit as well as novocaine ordinarily does, even when used in a 1 or 2 per cent solution.

4. As a spinal anesthetic I have observed the results in only 4 cases. These were likewise cases recently operated upon on the Bellevue Urological Service.

Dr. McLellan has called attention to the fact that in the majority of his spinal cases the blood pressure dropped rapidly from the start. As you will note in 3 of these cases, the blood pressures acted in quite the contrary manner, that is, they had a tendency to go higher. But this I attribute to a difference in technic in that on the Bellevue Service we are now giving 1 c.c. of ephedrine (50 mg.) at the time the skin is anesthetized for the introduction of the lumbar puncture needle. Then immediately after the anesthetic is injected into the spinal canal, another centimeter of ephedrine is given hypodermatically. In each case the blood pressure was taken before the first injection of ephedrine was given and the other blood pressure readings, recorded at five-minute intervals, were begun immediately after the patient was turned over on his back following the injection of the spinal anesthetic. The first case was a patient aged sixty-seven, on whom a prostatectomy (second stage) was done. His blood pressure before the anesthetic was given was 180/90. After the anesthetic was given the blood pressure readings were as follows: 190/80, 200/90, 210/90, 200/90, 200/90. The anesthesia was perfectly satisfactory and reached as high as the nin th rib inthe mammillary line.

The anesthetic was injected at 2:25 P.M. The anesthesia, tested by means of pin pricks, was still good at 5:30 P.M. and at 6:30 P.M. there was a slight return of sensation in his leg.

The second case, aged sixty-three, represents another prostatectomy (second stage). When the patient was put on the table the blood pressure was 150/90. Immediately after the anesthetic was given the blood pressure dropped to 100/60 at which juncture 1 c.c. of ephedrine was given. Five minutes later the blood pressure was 100/50 and five minutes later 70/50. Here 12 minims of adrenalin were injected by hypo. Five minutes later the blood pressure was 70/50 and then at five-minute intervals 90/70 and 110/80.

The anesthetic was injected at 2:00 P.M. and at 5:30 anesthesia was still present. At 6:30 P.M. there was slight evidence of return of sensation.

The third cases was merely a cystoscopic examination of a man aged fifty-seven. The first blood pressure was 120/90 and after the injection of nupercain, the blood pressure readings were as follows: 148/90, 148/90, 148/90, 150/90, 150/90, 150/90, 150/90. The anesthesia extended up to the eleventh rib in the mammillary line. It was given at 3:35 P.M. and was still present from the umbilicus down until 7:00 P.M. At 7:30 P.M. there was partial return of sensation.

The last case was a suprapubic prostatectomy. The first blood pressure was 115/60 and the blood pressure readings after the anesthetic was given were as follows: 120/70, 120/70, 118/65, 130/80, 138/80, 130/80, 130/80, 130/80, 130/80, 124/70, 120/70. The anesthetic was injected at 2:20 P.M. The anesthesia extended to the ninth rib. At 5:00 P.M. it was still present as high as the tenth rib and at 6:00 P.M. the highest point of the anesthetic was at the umbilicus. At 7:00 P.M. there was partial return of sensation.

In all of the cases the anesthesia was perfectly satisfactory and in no case were there any distressing or alarming symptoms whatsoever.

In closing I think it is only proper to call attention to Dr. McLellan's method of giving an epidural anesthesia which, to my mind, plays quite a part in the success of the procedure. Instead of using a long needle as many do, he employs a short needle, not over an inch long, and of small caliber. A needle of such length enables one to easily introduce the anesthetic just within the caudal canal which is apparently all that is necessary when a relatively large amount of solution is employed. It further obviates the danger of piercing the coverings of the spinal cord.

SODIUM AMYTAL

IN SURGICAL MANAGEMENT*

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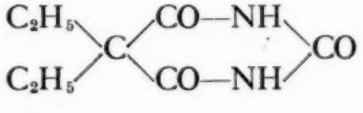
THE recent use of sodium amytal, which is the trade name for sodium iso-amyl-ethyl-barbiturate, as an intravenous anesthetic has caused a great deal of interest in the profession. We have for years looked forward to the possibility of a drug that would numb the sensorium and make the patient oblivious to his surroundings and yet not act in a deleterious way on any of the vital organs.

Thierfelder and von Mehring[1] in 1880 made the observation, which was later confirmed by others, that the sleep-producing action of alcohol was related to the number of ethyl groups present. A few years later Schmiedeberg conceived the idea of producing a nitrogen-containing hypnotic, knowing that intravenous injections of ammonia preparations raised the blood pressure. Schmiedeberg succeeded in preparing urethan; and, following in the order named, paraldehyde, amylene hydrate, sulphonal, trional and chloroformamide were produced.

It was then observed that the intensity of the hypnotic action of sulphonal depended upon the number of ethyl radicals linked to a central carbonatom, and for this reason Fisher and von Mehring in 1903 successfully completed the synthesis of a nitrogen-containing compound with the formula:



This substance was prepared by treating diethylmalonic acid ester with urea and sodium ethylate. The preparation was placed on the market under the name of "veronal," the generic name of which is "barbital."

Since that time a large number of barbital derivatives have been prepared, differing one from the other largely in the substitution of one or both hydrogen atoms by other radicals. It is possible to develop a great number of these substances.

In 1924 Fredet and Perlais,[2] two Frenchmen, succeeded in inducing general anesthesia with the barbituric acid series. They used a mixture of di-ethyl-allyl-barbiturate (trade name somnifene). This was administered intravenously. In 1927 Bumm,[3] following the lead of Fredet and Perlais, used a barbituric acid derivative intravenously. This compound he believed decomposed more readily than somnifene. He utilized sodium sec-butyl bromopropenyl barbiturate (trade name pernokton). He believed that the elimination of the pernokton was more rapid in the body and would permit a more rapid recovery from the anesthetic than would be possible with the other preparation.

In 1926 Page and Coryllos[4] used sodium iso-amyl-ethyl-barbiturate (trade name sodium amytal) to produce general anesthesia in animals. These animals went to sleep quietly and slept from two to six hours, and when they awoke they seemed fresh and showed no ill effects from the drug. A little later Page and Swanson[5] observed that the amytal stem was less toxic than the veronal.

In February, 1929 Zerfas and McCallum[6] of the Research Department of the Indianapolis City Hospital reported the successful induction with this drug of general anesthesia in man in about 300 cases. In

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September of 1929 Lundy[7] of the Mayo Foundation reported at the Pan-Pacific Surgical Congress 1000 cases, surgical and medical, in which this barbital derivative had been used.

Our experience with sodium iso-amyl-ethyl-barbiturate began in July, 1929. Up to the present time it has been administered in the clinic to 305 patients. Our experience with the drug and our observations upon this group of cases are as follows.

PREPARATION AND ADMINISTRATION

We have received from the manufacturer sodium iso-amyl-ethyl-barbiturate in crystal form, put up in ampules of 0.5 gm., 1 gm., and 1.5 gm. With each ampule we have received an accompanying ampule of triple-distilled sterile water, which when added to the anhydrous salt makes a 10 per cent solution. The accompanying ampule of water is added to the salt and the mixture is shaken gently until it is dissolved. Ten minutes should be allowed for the solution to reach the proper hydrogen ion concentration. A few times the solution obtained has not been clear, and this has been immediately discarded for another solution. We have given it only intravenously and at the rate of a grain and a half a minute. All of our patients have had a preliminary medication of $\frac{1}{6}$ to $\frac{1}{4}$ grain of morphine sulphate and $\frac{1}{150}$ grain of atropine sulphate one hour before the administration of the sodium iso-amyl-ethyl-barbiturate. Practically all of the patients have had the administration of the drug in the room. The usual precautions that are taken with general anesthetics of any kind should be taken with this one. The stomach should be empty, there should be no obstruction to the air passages, false teeth should be removed, and the chin held up. In one case of intravenous administration in which a considerable quantity of the solution was spilled into the tissues a sore arm resulted. The soluble salt in dilute solution may be injected intramuscularly or may be given by mouth or by rectum. With these last three ways of administering the drug we have had no experience.

In view of the fact that there are individual variations in the action of almost all drugs, we have felt that the intravenous administration of sodium iso-amyl-ethyl-barbiturate afforded the best method of controlling the dosage. There is a general feeling that the same amount of the drug given by mouth or rectum is safer, but we do not believe that this is true. Once the drug is absorbed by any method it is not recoverable, but when given by intravenous injection the effects can be watched and the injection discontinued immediately when the patient falls asleep or loses consciousness. In case the drug is given by mouth or by rectum the entire amount is not absorbed and the desired effect may not be produced. If, on the other hand, the patient is one of those individuals whose tolerance is rather low too large a dose may be given. We believe that the intravenous injection, which has allowed us to take into consideration the individual variation in the action of the drug is the safest procedure.

DOSAGE

The lethal dose for man is unknown. In dogs Page and Coryllos and others have found the fatal dose to be approximately twice the dose necessary for general anesthesia. As Zerfas and McCallum[8] have pointed out, man seems to be more susceptible to the anesthetic effects of the drug since he requires only one-third to one-half the amount per unit weight that is necessary for surgical anesthesia in animals.

There is a wide variation in individual susceptibility to the drug. The fact that the minimum dose required to barely erase consciousness varied frequently in our series from 3 grains to 9 grains illustrates how impracticable is any rule-of-thumb statement of dosage. In 1 case 17 grains were given before the patient lost consciousness, and in 5 more instances

12 grains each were required. This variation did not depend upon weight differences. In a few instances the resistance to the drug was attributed to accidental shortening of the interval between the preliminary morphine and the administration of the sodium amytal, but this could explain only a small group of cases. Factors of more importance seem to be the *age* and *general condition* of the patient. Thus old or debilitated people may fall asleep after 3 to 4 grains have been given, while young robust patients may require 7 to 9 grains before they lose consciousness.

For the first 50 cases we carried the patient beyond the stage of bare loss of consciousness and gave very large doses, 18 to 25 grains, and in one instance 28½ grains, in an attempt to secure surgical relaxation unassisted by other anesthetics; but we came to realize that the sodium barbiturate could not in the average case produce the desired surgical relaxation unassisted by other anesthetics. We therefore reduced the dosage, following the general rule of giving just twice the amount necessary to put the patient barely to sleep, so long as this did not exceed 22½ grains.

We feel, however, that this much is also unnecessary, so that now we stop the injection as soon as the patient falls asleep. In other words, at the present time we do not advise any more than a hypnotic dose, which takes out of the general anesthesia that excitement stage. However, we did not find the larger doses dangerous to the patient.

GENERAL EFFECT

By using a very small hypodermic needle attached to a 10 c.c. syringe the induction is not at all unpleasant. During the intravenous administration of the first 3 to 9 grains, in a room that is perfectly quite, the patient slips away into a sleep that certainly to appearances closely resembles the physiological. Except in 1 case, there was no evidence of an excitement stage, either during the induction of sleep by the sodium amytal or during the induction of deeper anesthesia by the superimposed inhalation anesthetics. In 8 instances the patient experienced laryngospasm, and with 3 of these patients the spasmodic coughing was so disagreeable that we stopped short in the administration of the drug.

The pupils become slightly contracted and in some cases fixed, so that they will not react to light. The corneal reflexes are diminished. The blood pressure in all but a few cases in our series fell, the systocil an average of 32 mm. of mercury, the diastolic an average of 16 mm., during the induction. It is worthy of note that this is the same average fall found in the first 165 surgical patients,[9] where larger doses were being given than in the last 100 cases. In other words, the average blood pressure fall is the same for bare induction of sleep as it is for deeper anesthesia. In some patients receiving as much as 18 grains of sodium amytal the blood pressure taken immediately at the completion of administration showed no reduction, while in others as little as 3 grains caused a systolic fall of 40 mm. of mercury. The greatest fall in systolic blood pressure was from 200 to 100 mm. of mercury. In 12 other instances the systolic fall was as much or more than 60 mm. In 5 of these instances the initial pressure was as high as 165 or more. In other words, it seems that a hypertension is more susceptible to reduction than is a normal blood pressure. In the large majority of these cases this reduction in blood pressure was so transient that the slightest motion or squirming on the part of the patient or the administration of inhalation anesthetic was accompanied by a restoration to normal. In no instance where ephedrine was administered early did it fail to restore the blood pressure.

The pulse rate, if elevated by emotional excitement, was reduced during the induction of the anesthesia. In all other cases, however, the pulse appreciably quickened after the injection of the sodium amytal. Respirations became shallow, and in some

cases the rate of respiration fell as low as 12 per minute. The color in all but a few cases has been uniformly good; in fact the complexion becomes rosy and sometimes resembles a febrile flush. The skin in most of the cases is dry, although in some there has been some moisture. The reflexes are diminished somewhat but never completely abolished.

THE PATIENT'S ATTITUDE TOWARD THE ADMINISTRATION

The reason we have continued the use of sodium amytal intravenously is because of the gratitude expressed by the patients who have received it. The most enthusisastic group are those who have had general anesthetics at some previous time. The ordeal of having to get onto an uncomfortable ward carriage, go to the elevator, be transferred to the surgical floor, and then from the ward carriage to be transferred to the operating table is more trying than we who have not been through it imagine. To get a glimpse of the operating room nurses and doctors all in white, and often to see and hear the rattle of the instruments as they are being transferred from one basin to another, and then to cap the climax to have something tight dropped over the mouth and nose to be relieved of all this is most gratifying. These patients state that instead of experiencing the most uncomfortable day of their lives, the day is passed without their knowledge, and when they awake late in the afternoon they find that the operation has been performed and they are safely back in their beds. Many of these patients, when told that the operation has been performed and that they are again back in their own room, are so much relieved that they will drop off to sleep again for two or three hours.

We have made it a practice to talk to these patients and to get their point of view, and it is because of their enthusiasm and because we feel that we have relieved them of a great amount of wear that we are more than willing to undergo the inconvenience that surrounds the administration of the drug. The necessity of having a special nurse for these patients, the occasional delay by the intern who administers the drug in the room, and the occasional dealy in obtaining supplementary anesthesia, because the shallow respirations slow the inhalation of the general anesthetic, are rather annoying to the busy surgeon who has been accustomed to the old regime; but we feel that the relief and satisfaction that the patient derives far outweigh these minor difficulties.

For a long time this result has been attempted with various agents, scopolamine being outstanding. Sodium iso-amyl-ethyl-barbiturate has the advantage that it is *sure* in the accomplishment of the result desired, and at the time more exact in the degree of stupor or unconsciousness that it produces. The effect is reached immediately upon injection, if the sodium barbiturate is given intravenously; and by observation of the patient's reaction to it as the drug is administered he can with safety be carried to any of three states, as desired, i.e., cooperative stupor, deeper unruly stupor or total unconsciousness. We believe that it should not be used to carry the patient beyond this third stage, i.e., deep *relaxed* unconsciousness. Another great advantage of the sodium barbiturate is the almost total elimination of postoperative nausea and vomiting. In general use we secure a cooperative stupor for regional and spinal anesthesia, and the further stage of unruly stupor or bare unconsciousness where inhalation anesthesia is to be superimposed.

In spite of our encouraging results with combined sodium amytal and spinal anesthetics, reported in a former article, we have been slow to administer the 2 agents in combination since each may produce a fall in blood pressure. However, we have, with ephedrine, sustained normal blood pressure in the 12 cases in which the 2 have been used. The types of supplementary anesthesia we have used are outlined in Table II, the types of operation in Table I.

TABLE I

REGION OR TYPE OF OPERATION	
Breast	25
Thyroid	37
Nose	9
Face	2
Eye	3
Mastoid	5
Mouth	8
Hand	1
Glands of neck	1
Gall bladder	24
Kidney	12
Shoulder	3
Laparotomy	5
Appendix	19
Stomach	5
Small intestine	5
Cecum, colon, rectum	17
Pelvis	45
Perineum	13
Hernia	9
Varicocele	2
Cystoscopy	2
Spleen	1
Parathyroid	1
Cesarian sections	3
Amputation of leg	1
Chest	1
Repair of nerve	1
Application of cast	1
Total	261
Medical cases	37
Obstetrical cases	7
Total	305

TABLE II

SUPPLEMENTARY ANESTHETIC USED	
$N_2O - O_2$ (85 per cent to 50 per cent)	28
$N_2O - O_2$ and ether	109
Local procaine or cocaine	15
Local procaine and $N_2O - O_2$	32
Spinal anesthesia	19
Ether	24
Total	227
Sodium amytal alone	34
Total	261

CONTRAINDICATIONS

We feel that debilitated or elderly people should not have sodium amytal, nor should patients with respiratory obstruction. Patients with a very high or very low blood pressure, being poor risks, should not be subjected to an additional drug. We are not so certain that the very small hypnotic dose that we are using at the present time would be contraindicated in pulmonary infection; however, we have not given it to any patient with a cough preceding the operation. In practically any case where there was some particular indication because of extreme nervousness on account of the impending operation we would be inclined to advise a hypnotic dose because there is very little reaction to a small dose except to throw the patient into a very quiet peaceful sleep.

UNTOWARD EFFECTS

During the administration of the drug in 3 instances there was a slight restlessness manifested and in 1 case a definite excitement stage, although in all the other patients the induction was quiet, and in these 4 patients quiet sleep was secured by an additional amount of the drug. Laryngospasm, which has occurred in 8 of our cases, was in 3 of these cases accompanied by severe coughing. This comes on almost immediately after the patient falls asleep and ceases when the dose is increased or within fifteen minutes after the injection of the drug is discontinued. This complication will not occur, it is believed, if the drug is in clear solution and of proper hydrogen ion concentration.

TABLE III

POSTOPERATIVE COMPLICATIONS	
Nausea	4
Vomiting	39
Headache	5
Restless reaction	14
Drunken delirium	1
Hysterical psychosis	4
Deep cyanosis	2
Catheterization up to fifth day	6
Catheterization once or twice	55
Involuntary urination	2
Bronchitis	1
Pulmonary edema	3
Backache	4
Sore arm (from injection outside vein)	2
Skin rash	1
Respiratory difficulty on table	9
Postoperative depression	3

As with other anesthetics, there is a relaxation of the tongue and pharygneal muscles, and the jaw must be held forward

to prevent the tongue from falling back and causing cyanosis and suffocation. For this reason we always keep a special nurse at the bedside until the patient has reacted. Since we have reduced the dosage to the minimum described above, the patient is often half awake shortly after the operation and a special nurse is not necessary.

On occasions when sufficient time has not been allowed for the drug to dissolve completely or when it has been injected too rapidly the respirations have become irregular. The patient takes four to eight deep breaths followed by a pause. Respiration becomes regular within ten to twenty minutes.

There are a few untoward effects which have been manifested *on the operating table* when the patient is receiving inhalation anesthetic after having had sodium iso-ethyl-barbiturate; but in no one of these instances could the entire blame be put upon the barbiturate, for such difficulties have arisen during inhalation anesthesia when the barbiturate has not been used. A few times the patient has stopped breathing for short intervals, and in other patients deep cyanosis has occurred. Respirations may be stertorous and difficult occasionally. At no time has there been a death on the table.

When returned to the room the patient as a rule lies motionless and does not awaken to full consciousness for from one to eighteen hours. Usually he awakens in from one to three hours and is fully conscious in from six to ten hours. We have adopted the routine of giving a hypodermic injection of 7½ grains of caffeine sodium-benzoate and ⅜ grain of ephedrine sulphate during or just after operation if we feel there is any possibility of cerebral anemia or passive congestion from loss of circulatory tone.

The chief complication to be feared is pulmonary congestion, due to the shallow respirations, particularly was this possible in those patients early in this series who received large doses and lay motionless for hours. All 3 of our cases of pulmonary edema were in the first of the series, where the larger doses were given. One of these patients developed frank pneumonia and died. As a prophylactic measure against this complication we now routinely ventilate the lungs with a mixture of 5 per cent carbon-dioxide and 95 per cent oxygen before the patient leaves the operating room and repeat this in the bedroom if the patient is slow in reacting. As soon as he reacts he is encouraged to take five or ten deep breaths at least once an hour.

When reacting from the anesthetic 6 per cent of our patients were more restless than normal, and one required a restraining sheet. Although in a twilight stupor, if such a patient is reassured, he will usually drop off to sleep again and awaken quietly several hours later. Morphine should be given early for such conditions. Sometimes the restlessness is due to overdistention of the bladder, and catheterization will be sufficient to quiet the patient. Twenty-one per cent of our patients have been catheterized once or twice and 2 per cent up to the fifth postoperative day. The large number of catheterizations is due in large part to the fact that all women who have received the drug are catheterized eight hours after the operation if they have not voided by that time. Three of these patients have developed cystitis, transient in nature.

One man, an alcohol habitué, reacted in a drunken delirium lasting eight hours, and 4 women developed depressive psychosis lasting several days. Two of these 4 were the only patients in the series who did not like the drug. Several patients complained of bad dreams.

There have been 9 hospital deaths in the surgical series and 3 in the medical. Excepting the case of postoperative pneumonia already mentioned, the cause of death was clearly explained without relation to the sodium iso-amyl-ethyl-barbiturate.

As far as traced, we have seen no *late* untoward effects from the drug.

CONCLUSIONS

Sodium iso-amyl-ethyl-barbiturate used as a *preanesthetic*, with a dose just large enough to make the patient lose consciousness, has given us more satisfaction than any other drug we have used. In patients with Graves' disease and in those who are nervous, sensitive, or apprehensive it gives the most satisfying results. If given slowly and intravenously and the dose stopped as soon as the patient loses consciousness, we do not believe that one will ever experience any serious untoward effects.

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VAGINAL SPECULUM AS INDIFFERENT ELECTRODE*

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THERE are many lesions of the cervix that are better treated by electrocoagulation than by galvanocauterization. For several years I have used the vaginal speculum as the indifferent electrode, connecting it by a snap arrangement to one of the leads from the diathermy apparatus. The advantages are ease of application, eliminating an extra piece of apparatus, and making snug and even application of a broad metallic surface to a moist mucous membrane. The danger of sparking the patient, as may happen with a poorly placed lead plate to the buttocks or abdomen, is eliminated.

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CLINICAL OBSERVATIONS ON THE RELATION OF SODIUM AMYTAL TO VASOMOTOR AND DIURETIC PHENOMENA AFTER ORAL ADMINISTRATION*

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ANY drug which will produce sufficient hypnosis to spare the patient the dread of an operation without endangering, at the same time, the patient's life, or without creating difficulties in inhalation anesthesia, or without obscuring postoperative manifestations, must be welcomed as a desirable adjunct to preanesthetic medication. The barbituric acid derivatives as a group have been acclaimed to possess these properties in varying degrees. Their individual behavior is therapeutically and pharmacologically similar in every respect except that the degree of toxicity differs with each derivative.

Experimentally, diethyl barbituric acid or barbital (veronal) has the lowest toxicity or the widest safety margin (Eddy 1928,[1] Weiss 1929[2]), while the more complex derivatives present higher degrees of toxicity or lower safety margins. Apparently, the speed and degree of hypnotic efficiency of the individual derivative are somewhat proportionate to its degree of toxicity. In animal experiments, the derivatives which produce the most efficient and rapid hypnosis amounting to deep anesthesia have also proved themselves to be the most toxic (Eddy 1928[1]).

There are today a number of barbituric acid derivatives on the market offered under various trade names, such as barbital, veronal, allonal, ipral, phanodorn, pernocton, somnifene, luminal, dial, neonal, amytal and their respective sodium salts. For each there has been claimed a particular anesthetic virtue when used in sufficiently large doses. In all fairness one must say that such virtues exist. At the same time one must take into consideration experimental evidence pointing to the dangers accompanying the use of all of these drugs. With the introduction of each of these drugs, invariably an enthusiastic group of supporters has made special claims for the anesthetic value of the particular derivative, later to be followed by less enthusiastic reports based on intensive observations by the more cautious. The controversies on somnifene in the French literature between 1924 and 1926 and on pernocton in the German reports of 1927 to 1929 are typical for divergence of opinions. Although the pharmacologists of this country have for a number of years used the barbiturates for their anesthetic properties in animal experimentation, clinically they had not been used on a large scale for anesthetic purposes until about 1928. Recently interest has been evinced in the action of sodium isoamylethyl barbiturate appearing under the trade name of sodium amytal, and courteously offered by the manufacturers to a number of investigators for clinical and experimental observations.

At the Stanford School of Medicine we recently have been supplied with a sufficient amount of the drug for detailed studies. Holman reports the results of his observations in general surgical procedures in the present issue of this journal. We wish to add certain observations on gynecological and obstetrical patients, which form part of a study of the clinical value of barbituric acid derivatives as anesthetic adjuncts. Studies in changes of blood pressures, diuretic phenomena including sulphophenolphthalein excretions and toxic phenomena are the particular points discussed in the following paragraphs.

We accept without comment the dramatic and highly hypnotic action of sodium amytal as originally stated by the various

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observers of the Indianapolis group.[3] Our aim in this study is a search for more minute information regarding dangers following the administration of the drug. In the earlier part of our acquaintance with sodium amytal we followed, in regard to its administration, the original recommendations made by Zerfas and McCallum.[3] Like everybody else, we were then greatly impressed by the dramatic action of the drug. Later it was decided to administer the drug by mouth, and since no material difference was observed in its general action hypodermic administration was abandoned for the more simple oral medication. With the exception of obstetrical patients, most of our observations presented here were made after this period. Our technic of administration was essentially this: About one-half to one hour before operation the patient, designated as Group A, received 15 grains of sodium amytal by mouth. In addition, one-sixth to one-fourth of a grain of morphine sulphate was given hypodermically prior to taking the patient to the operating room. The only clinical difference between intravenous and oral administration, aside from being able to gauge the dose slightly more accurately, is the speed and length of the reaction. After oral administration the maximum reaction appears from five to ten minutes later and is slower in wearing off in the postoperative period.

In another group used for comparative studies in diuretic reaction, designated as Group B, sodium amytal was replaced by scopolamine. In this group the patient received 1/300 of a grain of scopolamine hypodermically one hour before the operation and again thirty minutes later. In addition, one-sixth to one-fourth of a grain of morphine sulphate was administered hypodermically prior to sending the patient to the operating room.

In 21 patients we have studied the immediate and more remote effects of sodium amytal and morphine on blood pressure. We found essentially the same reactions as reported by other observers for intravenous administration of the drug. In 19 patients the systolic pressure dropped from a few millimeters to 40 mm. within ten to twenty minutes after the sodium amytal had been taken by mouth, while the diastolic pressure usually decreased from 10 to 15 mm. occasionally falling from 20 to 25 mm. for a period of about twenty minutes. Toward the end of an hour the systolic pressure usually had risen to within 50 per cent or more of its primary drop, the diastolic pressure remaining essentially the same. Only once did we see the pressure rise above the normal after thirty minutes, and once it remained practically stationary.

Operative procedures were begun from thirty to sixty minutes after the ingestion of the drug. Regardless of the age and weight of the patient or the length of the operation we have observed that during the operation in the majority of instances the systolic and diastolic pressures rose from 10 to 20 and occasionally 30 mm. above the average normal pressure. Frequently this was accompanied by a rise in pulse rate from 10 to 20 beats over the normal, although respiration remained unaltered or slightly depressed as observed by others. Just how to interpret this phenomenon we do not know, but do not believe it to be due to the added effect of morphine since the blood pressure promptly returns to a normal level after the termination of the operation. It is possible that the body position has to do with the reaction since we operate on our patients in a 30° Trendelenburg position. We also supply the patient with fluid by hypodermoclysis during the entire duration of the operation. This, too, may have a bearing on the sudden increase in pressure. We doubt that operative manipulation has anything to do with this phenomenon since we have reduced the handling of tissues to a minimum, paying particular attention to the avoidance of any pulling on the pelvic viscera. We are under the impression that patients operated upon

TABLE 1

BLOOD PRESSURE OBSERVATIONS BEFORE, DURING, AND AFTER OPERATION. THE PERIOD OF OPERATION IS MARKED BY A HEAVY LINE AT EITHER END

Name	Basic B.P.	10″	20″	30″	40″	50″	1 hr.	1′15″	1′30″	1′45″	2 hrs.	2′15″	2′30″	2′45″	3 hrs.	3′30″	4 hrs.
AN	184/90	174/94	138/70	134/68	134/76	134/70	150/90	.....	.....	.....	105/60	.....	110/60	.....	120/80	.....	108/60
RR	120/78	115/80	.....	100/80	90/70	.....	95/70	100/82	140/80	160/95	150/90	130/100	135/95	130/95	128/80	140/90	125/80
MN	116/64	92/60	100/72	.....	125/85	120/80	100/70	110/70	120/80	140/90	140/90	130/90	140/90	140/90	120/80	120/80	104/60
KE	134/86	100/70	96/74	94/76	94/70	.....	.....	.....	140/95	145/100	165/110	140/100	135/95				
CS	174/100	150/?	98/?	125/?	140/110	.....	140/110	.....	150/105	150/100	155/100	160/100	170/95	.....	170/100		
BI	118/78	102/80	.....	100/70	.....	.....	100/70	120/100	.....	110/90	.....	100/80	.....	110/80	.....	.....	118/76
BN	116/78	106/65	.....	100/60	.....	110/70	130/75	125/75	110/65	.....	106/65	.....	.....	.....	100/60		
MN	132/94	92/68	.....	86/60	.....	120/100	150/120	145/110	140/110	135/95	140/100	.....	.....	.....	140/100		
KT	110/80	100/80	100/80	.....	98/80	120/90	125/95	130/100	130/105	135/100	125/95	110/90	100/85	125/95	120/100	115/100	115/95
HY	110/70	100/60	90/50	100/60	96/112	.....	100/60	.....	110/80	105/80	105/80	.....	105/80	.....	96/84		
DS	100/60	104/55	102/57	80/58	80/?	90/50	108/58	.....	120/60	.....	130/90	.....	125/95	.....	110/90		
BN	114/80	94/66	88/62	102/80	96/72	110/88	90/60	.....	110/80	.....	110/75	.....	120/90				
KY	118/70	.....	118/70	118/70	128/80	120/70	125/80	.....	110/70	.....	.....	.....	.....				
BR	170/112	136/110	155/118	190/130	160/120	154/116	152/116	135/100	.....	155/100	.....	190/100	165/100	160/100	160/112	.....	160/112
EY	140/76	118/80	110/70	124/70	136/90	130/90	.....	135/95	.....	140/95	130/90	140/95					
SE	110/60	82/?	72/?	68/?	84/?	110/60	.....	128/65	.....	110/60	.....	115/60	.....	.....	110/65		
BT	122/88	98/66	90/65	110/75	105/70	105/70	110/80	120/90	130/100	120/85	130/100	135/110	140/90	140/100	140/105	.....	105/70
KE	124/84	100/64	80/2	100/80	110/74	.....	84/50	90/50	110/70	130/95	90/50						
IN	146/94	128/72	102/66	110/74	120/90	150/120	180/115	170/120	175/120	165/110	.....	.....	.....	.....	150/95		
OE	124/76	104/69	100/70	102/84	100/70	105/75	105/80	105/85	110/85	108/65	110/65	112/70	112/70	.....	90/62		
DY	105/78	100/75	98/75	85/70	105/80	.....	85/70	.....	105/80	.....	105/85	.....	.....	.....	106/80		

under scopolamine and morphine do not present this rise of pressure, although we have not made an intensive comparative study. This change in blood pressure has particularly interested us since Zerfas and McCallum[4] and Lundy[5] have apparently not encountered it in their large series. It will need further comparative studies before we will permit ourselves to come to any conclusions. We can state, though, that this particular rise in pressure has not given us any trouble in hemostasis.

We have nothing to add to the present knowledge of the influence of sodium amytal on respiration and pulse rate. There is no doubt that respiration is depressed by the amount we have used orally, necessitating at times the use of caffeine sodium benzoate which, when given in sufficiently large doses to counteract the depressing effect of sodium amytal, also defeats the hypnotic action of the drug to a marked degree. An alarming collapse of the vasomotor apparatus we have seen only once in our entire experience. This occurred in a patient whom we had slated for an abdominal operation because of miscarriage from a double uterus. The patient passed the gestation product while being prepared in the operating room and the product was removed intact from the cervix without any particular bleeding. After the patient was returned to her room the pulse rate and temperature rose within a few minutes to 160° and 105°F. respectively in the entire absence of symptoms of shock and bleeding but in the presence of marked cyanosis and respiratory depression. Since no instrumentation took place and bleeding was very slight, we ascribed this to the action of sodium amytal, particularly so since pulse, respiration and temperature returned to normal within a few hours after vigorous counter measures had been instituted.

In various instances of respiratory depression early during the inhalation anesthesia ephedrine and caffeine both had to be used. To our way of thinking the necessity of having to resort to counterstimulants frequently is a decided drawback to this particular barbiturate. We found it rather disturbing that our vigilance over the patient during twenty-four hours after the ingestion of the drug had to be increased to a degree where it became a burden to those connected with the supervision of the patient. It cannot be denied that while deep hypnosis lasts anesthetists, assistants and nurses are in a state of uneasiness. Although the patient may be most grateful for having been spared the dread of the operating room and the fear of pain often following immediately after awakening from the anesthetic, the added work for the attendants is a disturbing factor and requires further search for the ideal dosage or the use of a less toxic barbiturate.

Severe confusion following the use of sodium amytal we have encountered in three instances. On the other hand visual disturbances, lack of orientation, restlessness, and latent intestinal consciousness are present in one form or another in about 25 per cent of all patients observed by us. It was of particular interest to us that restlessness, with accompanying insomnia and intestinal consciousness in the absence of distension, was latent. This rarely appeared until the second or third day and at times was very annoying to the patient. Making allowance for the action of pantopon, which we used exclusively as a postoperative narcotic, we still believe that the sodium amytal is responsible for these phenomena for they are absent in our scopolamine group. The latent clinical manifestations cited here may be connected with lagging excretion of the drug similar to barbital, which has been shown experimentally to be excreted slowly over a period of several days (Gower & Tatum, 1929).[7]

Our experience with a combination of regional anesthesia, using novocaine 2 per cent, and sodium amytal by mouth, has been very disappointing. Following the injection of novocaine the patient becomes restless in spite of additional

nitrous oxide inhalation. Experimental evidence has proved in animals that the two drugs have an antagonistic action which in our experience seems to hold good for man, although Zerfas and McCallum[4] report satisfactory results from regional anesthesia when sodium amytal given intravenously is used in conjunction with novocaine. Since any barbituric acid derivative apparently is equally efficient in counteracting the toxic effect of the members of the cocaine group we do not see any particular reason for using sodium amytal for its detoxicating action alone. We have found that barbital, for instance, will serve the same purpose, and when given judiciously in divided doses together with sodium bromide, will also produce a sufficient state of hypnosis to alleviate the dread of the operation with an added advantage of a much greater safety margin in toxicity. We are studying at present the usefulness of this drug for its preanesthetic value when combined with scopolamine and pantopon, and so far we are well satisfied with the results. It has been our experience that a sodium amytal patient, even under nitrous oxide anesthesia, frequently becomes restless as soon as the novocaine takes effect. This reaction was sufficiently lasting to be annoying to our anesthetists. We also were under the impression that hypnosis was definitely lightened by the amount of novocaine used by us. We therefore have abandoned this combination as unsatisfactory.

Our results of the use of 6 to 7½ grains of sodium amytal given intravenously in labor corresponds to the observations made by others.[6] The drug efficiently provides a period of rest of from one to three hours, but beyond that does not offer any advantages over other barbiturates. Blood pressure reactions are essentially the same as recorded here except that the drop is not as pronounced and not as lasting. An increased pulse and a decreased respiratory rate are invariably seen. The fetal heart rate, after allowing for its variations during uterine contractions, does not seem to be influenced. In repeated doses the reactions in the mother are the same. We have been wondering whether this holds good for the fetus. In two instances the heart rate slowed down materially after the second dose, necessitating immediate delivery. One child was stillborn and the other markedly asphyxiated, later dying of nonspecific hemorrhagic disease of the bowel. In either case we do not care to charge the end-result to the action of repeated doses of sodium amytal given intravenously, but call attention to the possible relation of repeated doses to a collapse of the vasomotor system of the fetus.

Recently we have interested ourselves in the relation of sodium amytal to diuretic reactions. Earlier casual observations seemed to suggest a retardation of fluid output. We, therefore, undertook to study two groups of patients submitting to operations of essentially the same type and severity. In Group A we have placed 19 patients having received sodium amytal and morphine, and in Group B 17 patients having received scopolamine and morphine according to the method of administration previously stated. With few exceptions routine hypodermoclysis during the entire length of the operation was used to establish a fluid balance, about from 1000 to 1500 c.c. being allowed to accumulate in the tissues of the thighs. Readings on fluid intake and output were then recorded for each twenty-four hours on three consecutive days beginning with the start of the operation. Vomiting is very rare in sodium amytal-morphine patients and uncommon in scopolamine-morphine patients, although nausea is often present in the latter group. We have excluded the occasional vomiting patient from this study. In the following tables and charts our observations are recorded in actual figures and graphic expression:

In the interpretation of these tables and charts one naturally must make allowance for the great variability in the constant of fluid intake and output. One, furthermore, should make allowance for all possible

TABLE II

SODIUM AMYTAL AND MORPHINE

TOTAL INTAKE AND OUTPUT ON THREE INDIVIDUAL DAYS, INCLUDING THE DAY OF OPERATION

Day of Operation			First Day P.O.		Second Day P.O.		Day of Operation	First Day P.O.	Second Day P.O.
Name	Intake	Output	Intake	Output	Intake	Output	Per Cent	Per Cent	Per Cent
	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.			
BN	810	690	600	580	760	720	85.19	96.97	94.74
KT	1520	670	1170	495	1020	1080	44.08	42.31	105.88
MI*	1550	265	1140	210	2550	1671	17.10	18.42	65.53
IN	2100	470	1800	420	1500	900	22.38	23.33	60.00
AN*	2220	300	2520	330	2250	1200	13.51	13.10	53.33
KE	2220	760	1980	800	2400	1230	34.23	40.40	51.25
BI*	2610	630	1560	1380	2040	2070	24.14	88.46	101.47
BT*	2630	1380	2340	1740	1800	2130	52.47	74.36	118.33
HY*	2640	420	1530	720	1560	1290	15.90	47.06	82.69
EY*	2900	430	2100	1050	1680	900	14.83	50.00	53.57
BR*	2940	240	2030	780	1740	900	8.16	38.42	51.72
SE*	2960	600	3600	1170	3210	1890	20.27	32.50	58.88
ME*	3000	100	3160	840	1770	930	3.33	26.58	52.54
RS*	3280	600	1500	630	1890	570	18.29	42.00	30.16
KE*	3290	750	1410	1020	1650	1020	22.80	72.34	61.82
BN*	3290	630	1650	1560	1560	900	19.15	94.55	57.69
MN*	4390	660	1900	1080	3260	1650	15.03	56.84	50.61
CS*	4605	420	2070	1290	2070	1200	9.12	12.33	57.97
DS*	4630	840	1560	1170	1640	720	18.14	75.00	43.90

* Indicates routine hypodermoclysis during operation.

variations depending upon age and type of patient, length and severity of the operation, and the recuperative faculties of the individual. It, therefore, is essential that one disregard the single observation because of the individual variation, and limit this study to group reactions.

Patients having received sodium amytal and morphine as a preliminary to inhalation anesthesia take in more fluid in the twenty-four hours following the operation than do patients having received scopolamine and morphine. At the same time urinary output is actually and relatively decreased in the sodium amytal group. Our original figures, not detailed here, show that sodium amytal patients take fluid by mouth more readily on the day of and the day following the operation because of the greater freedom from nausea.

In the second twenty-four hours the fluid intake in both groups reaches fairly equal levels, but the ratio of output again presents a lower average in the sodium amytal group. In the scopolamine group the urinary output at times exceeds the fluid intake during this period. This is of interest because the same phenomenon does not appear in the sodium amytal group until twenty-four hours later.

In the third twenty-four hours the average fluid intake of the sodium amytal group rises slightly above the scopolamine group, while the ratio of output to intake reaches more similar levels.

Our observations recorded in Table IV, the figures of which are graphically

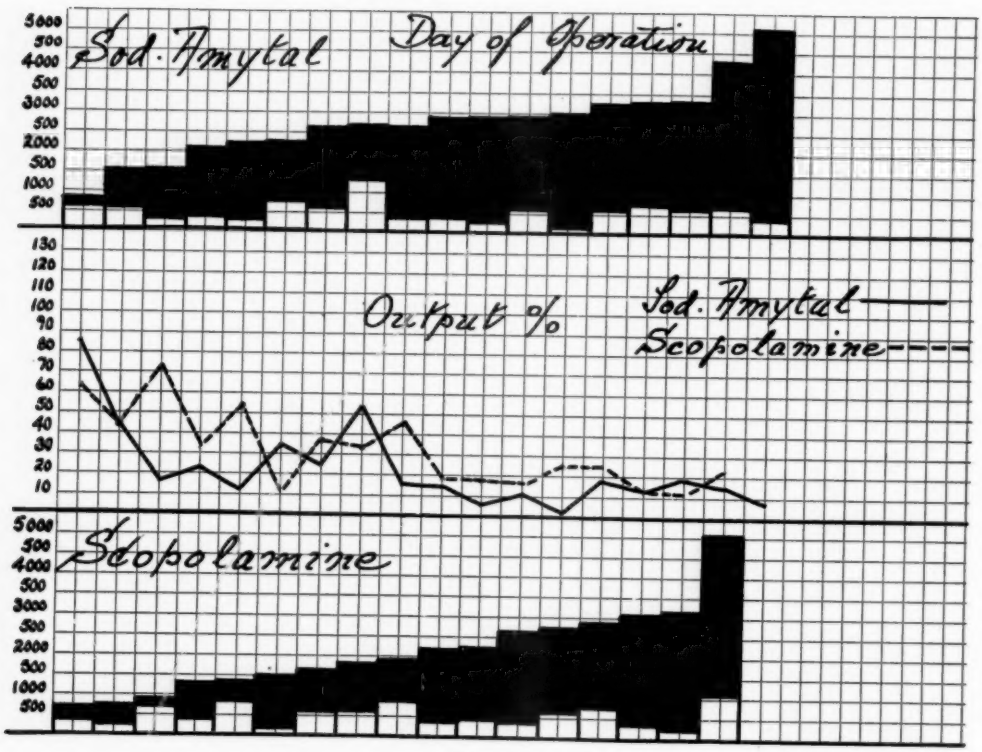
Sod. Amytal
Day of Operation
Output %
Sod. Amytal
Scopolamine
Scopolamine

FIG. 1.

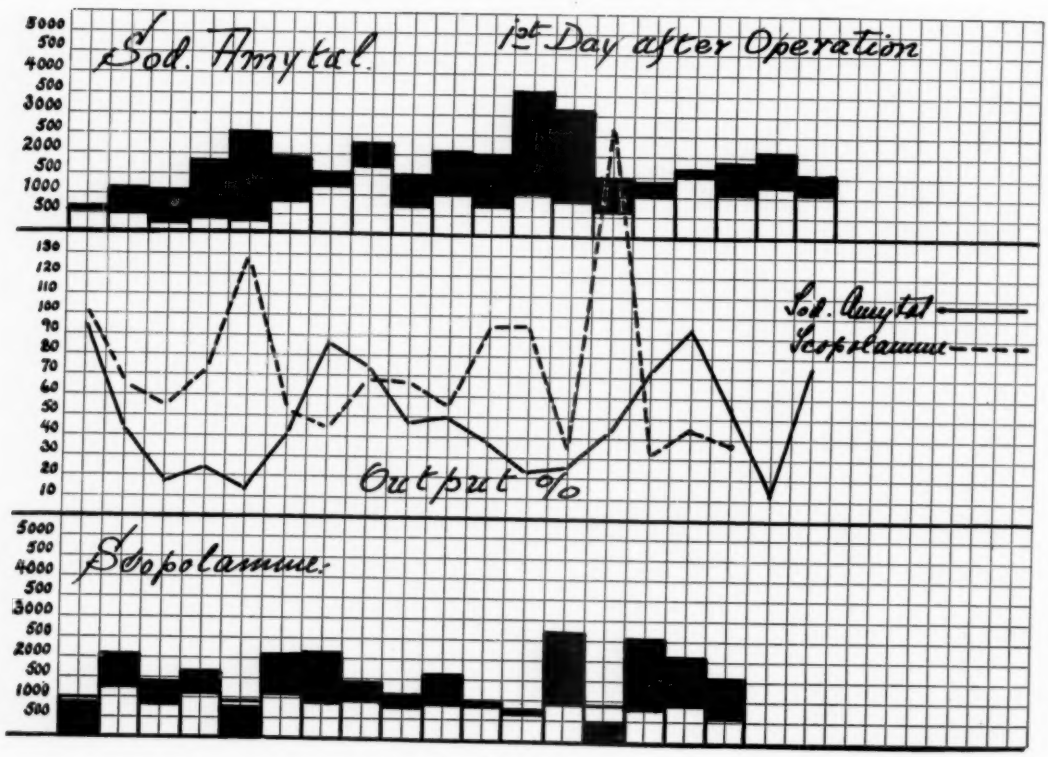
Sod. Amytal.
1st Day after Operation
Output %
Scopolamine.

FIG. 2.

TABLE III

SCOPOLAMINE AND MORPHINE

TOTAL INTAKE AND OUTPUT ON THREE INDIVIDUAL DAYS, INCLUDING THE DAY OF OPERATION

Day of Operation			First Day P.O.		Second Day P.O.		Day of Operation	First Day P.O.	Second Day P.O.
Name	Intake	Output	Intake	Output	Intake	Output	Per Cent	Per Cent	Per Cent
	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.			
FR*	650	410	930	950	1200	1400	63.08	102.15	116.67
RL	750	330	2050	1350	2200	1350	44.00	65.85	61.36
PR	930	720	1480	810	1620	950	72.42	54.73	58.54
SN*	1340	420	1640	1170	incomplete		31.34	71.34	
RE	1440	780	700	900	1500	1120	54 17	128.57	74.67
CN*	1500	150	2080	1110	1680	240	10.00	53.37	14.29
KL	1665	630	2115	900	2250	2010	37.84	42.55	89.33
FE*	1750	570	1430	990	incomplete		32.57	69.23	
LS*	1800	840	1160	780	1900	1100	46.67	67.24	57.89
TT*	2265	440	1630	897	1530	1620	19.43	55.03	105.80
BA*	2440	480	945	900	1095	1065	19.67	95.24	97.26
CS*	2600	390	750	720	960	600	15.00	96.00	62.50
HN*	2720	660	2720	900	780	540	24.26	33.09	69.23
KY*	2830	720	480	930	1590	900	25.44	193.75	56.60
LH*	3060	375	2520	775	2100	1320	12.25	30.75	62.86
CN*	3225	355	2130	960	1950	840	11.01	45.07	43.07
AN*	5060	1020	1560	600	1740	600	21.60	38.46	34.00

* Indicates routine hypodermoclysis during operation.

expressed in Chart IV, give the total results of fluid intake and urinary output during the three days referred to here. The graphic chart clearly shows the great variation in individual fluid intake in both groups with a persistently higher intake in the sodium amytal group. The curves otherwise run a fairly parallel course. The output curves, aside from a few variations, also simulate each other with an apparently slightly higher level in the sodium amytal group. While in this group there is apparently a greater output, it is only relative, for when compared to the intake, as expressed graphically in the percentage curve of Chart IV, it is actually lower in the general average. In other words, when one compares all factors cited here one cannot help but feel that sodium amytal, while it favors a greater fluid intake because of the absence of nausea, depresses and retards diuresis when compared to similar studies with scopolamine. The possibility of a depression of water metabolism (Barbour, Hunter, and Richey [9]) due to morphine exists in both groups in about equal proportion and while, perhaps, an individual factor, becomes, therefore, negligible in its importance in a group study such as this.

Barbital is excreted almost entirely through the kidneys. Its excretion is slow, taking from two to three days to be eliminated (Paolini 1928, Gower and Tatum 1929, Eddy 1929[7]). There seems to exist a selective fixation for barbital in the nervous system and the blood corpuscles, which may explain the prolonged period of excretion (Pucher 1925, Fabre et Fredet 1925, Paolini 1928[8]). Since the pharmacological reactions of the barbituric acid derivatives are essentially the

TABLE V

SULPHOPHENOLPHTHALEIN EXCRETION BEFORE OPERATION, ON THE DAY OF OPERATION, AND DAY AFTER OPERATION

		SODIUM AMYTAL AND MORPHINE								SCOPOLAMINE AND MORPHINE						
		Before Op.		Day of Op.		Day after Op.				Before Op.		Day of Op.		Day after Op.		
Name	Age	C.c. Urine	Per Cent Ph Th	C.c. Urine	Per Cent Ph Th	C.c. Urine	Per Cent Ph Th	Name	Age	C.c. Urine	Per Cent Ph Th	C.c. Urine	Per Cent Ph Th	C.c. Urine	Per Cent. Ph Th
AN	61	700	42	95	37	125	30	CN	40	205	40	70	37	350	58
MN	40	320	47	270	27	250	30	BH	47	620	45	80	48	80	60
IN	40	450	47	100	28	170	41	TT	43	560	52	110	35	267	67
KY	23	450	53	110	53	400	42	RL	33	750	58	60	4	320	55
KT	36	460	55	60	15	325	50	SH	47	130	58	50	47	50	31
BN	38	550	59	80	27	125	50	CS	38	600	50	80	38	350	42
BR	30	480	57	100	40	220	42	FR	65	1225	59	115	52	100	45
EY	42	600	57	100	45	90	80	KY	42	725	60	70	28	470	61
RS	27	580	58	150	20	430	40	FE	25	1050	60	220	35	375	68
HY	33	510	58	115	40	300	55	RE	34	1230	60	90	50	350	50
SE	36	525	58	100	50	160	30	PR	24	960	65	80	35	265	47
KTE	56	820	61.5	400	50	350	40	CL	29	960	65	80	35	280	47
DS	28	575	65	110	35	200	50	SN	24	410	65	175	55	430	60
KE	45	475	65	90	35	400	48	HN	33	675	73	135	70	100	90
MI	22	600	67.5	260	45	410	50	LS	50	950	98	72	27	400	88
BT	43	675	73	135	20	240	60								

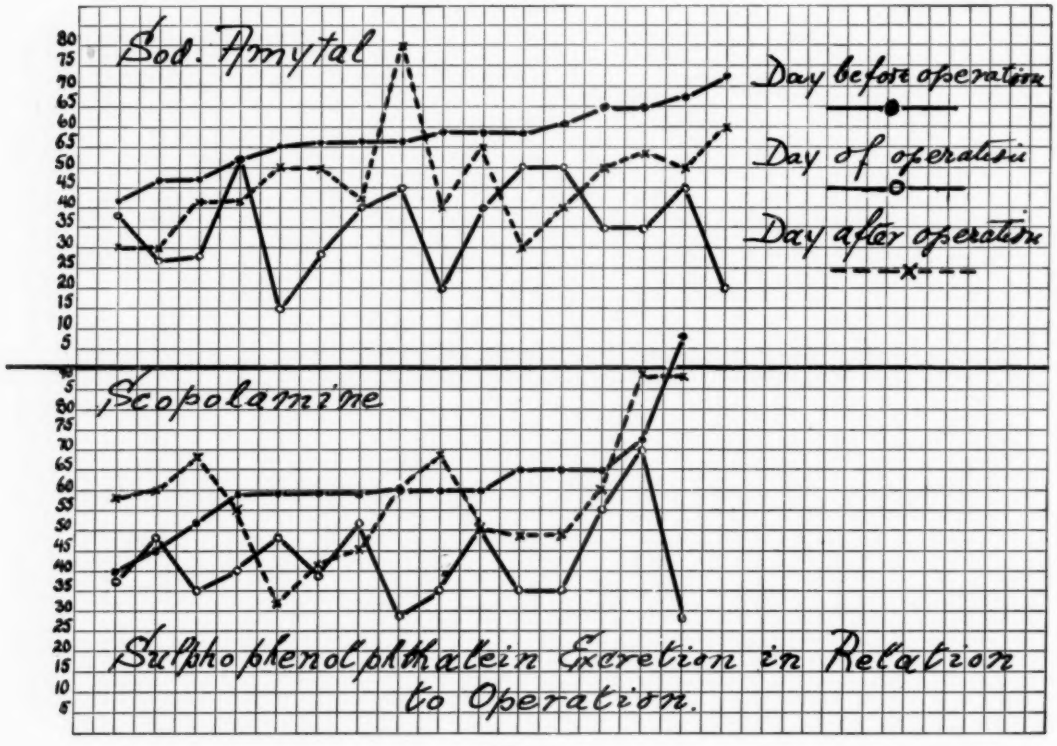

FIG. 5.

ing the normal. The dissimilarity between the two groups at this period is again negligible. If we may use this test as an indicator for glomerular activity we might conclude that the diuretic depression and retardation observed by us clinically is not the result of the action of sodium amytal on the glomerular apparatus but

rather a tissue manifestation expressing itself in a reluctance to give up stored fluids because of a depression of the vasomotor system. Such an assumption would fit more readily in with the observations made on latent excretions of barbital.

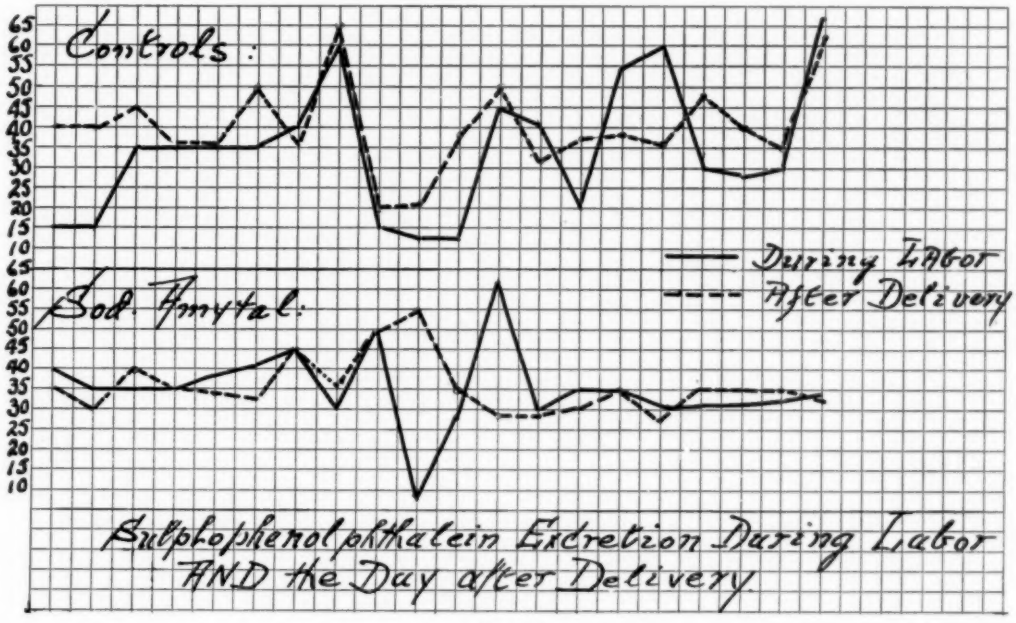

Fig. 6.

Recently we attempted a similar clinical study in parturient women. It was at once obvious to us that diuretic studies embracing intake and output offered insurmountable obstacles because of the upsets of labor. But we carried out a comparative study on sulphophenolphthalein excretions during and following labor without establishing a previous normal. Twenty-one patients received from 6 to 7½ grains of sodium amytal intravenously in the first stage of labor after the sulphophenolphthalein test had been done. The second stage of labor was managed under nitrous oxide analgesia. The test was repeated after twenty-four hours. The results, when compared to an equally large group of controls, express an absence of any influence of sodium amytal on the glomerular activity, which in accordance with our previous observations.

Our conclusions are that sodium isoamylethyl barbiturate or sodium amytal, when given in conservative doses is an efficient hypnotic. Because of its narrow safety margin it is not a desirable drug when the degree of hypnosis required depends upon a dosage which approaches 50 per cent of the minimal lethal dose for animals. When used solely for the purpose of preanesthetic hypnosis, while efficient, it is not superior to other barbituric acid derivatives possessing greater safety margins.

There is no particular advantage of intravenous over oral administration except that in the former hypnosis is more rapid and perhaps of shorter duration in the postoperative period.

A combination of oral administration and regional anesthesia with novocaine has been unsatisfactory in our hands. We believe that the detoxicating effect of sodium amytal on the cocaine derivatives is also accompanied by a reversed action in which the latter group of drugs counteracts the hypnotic depths produced by sodium amytal. The sole use of the drug for the purpose of counteracting the toxicity of the cocaine group, while efficient, is of no advantage since the same can be achieved by the administration of barbital by mouth.

them. A larger dosage of sodium amytal intravenously administered induces a very definite and conclusive condition of analgesia. It has seemed to us that the sleep-producing possibilities of sodium amytal are superior and more to be desired than is the full analgesic effect. Sodium amytal and the supplemental use of ether, ethylene, nitrous oxide, spinal anesthesia, regional or local anesthesia, give a highly satisfactory and complete even anesthesia.

We have used sodium amytal alone or supplemented by other anesthetic agents in the following surgical conditions (Chart 1):

The effect of sodium amytal intravenously can be best indicated by describing a more or less typical case in which the drug is administered. The patient weighs 110 lb., has an hyperthyroidism of Graves' disease, with a basal metabolism of +80 and all the clinical signs of hyperthyroidism are present. The patient is marked nervous and emotionally agitated. She has been at rest in bed under proper preoperative treatment for a week. The operation is scheduled to begin at 8:30 A.M. On the day of the operation no breakfast is given, and at 8:15 A.M. the interne enters the patient's room and states that he is about to give her a treatment. A 10 per cent solution of sodium amytal is prepared and 100 mg. of the drug, or 1 c.c. of the 10 per cent solution is given every minute. After three and a half to four minutes the patient may state that she is becoming drowsy or becomes somewhat loquacious. At about four and a half minutes, the patient takes a deep sigh or yawns, and at about six minutes passes into a sleep. From six to nine minutes the breathing is rather shallow, the color good, the pulse about the same as at the beginning of the injection, although it may be somewhat slower. At about nine minutes the respirations increase in amplitude and the patient either snores or has the breathing typical of very deep slumber. The patient may or may not be roused but she is still sensitive to pain when the tissues are clipped with a towel clip. The patient is allowed to remain at rest for another three to five minutes before being transported on a stretcher to the operating room. The patient is transferred to the operating table, elevated into the proper position, the field sterilized and draped. Before the operation is begun, the degree of analgesia is determined by pinching the skin. If the patient reacts, ethylene is then administered. In the majority of cases the ethylene may be discontinued or lightly administered during the remainder of the operation. At the conclusion of the operation the patient is returned to her bed and she sleeps anywhere from two to eight hours. In 80 per cent of the cases the patient gradually awakens as if after a quiet sleep. In about 20 per cent, of cases there is some increased irritability and restlessness. A sixth of a grain of morphine will adequately control this manifestation.

The instructions call for the giving of 1 c.c. of the solution containing 100 mg. per minute. Lately we have been giving it a little more slowly than this, feeling that we obtain a more gradual unconsciousness and that the analgesic properties are thereby increased. We have used sodium amytal with almost every variety of anesthetic agent and ether may be used after sodium amytal has been given without any preliminary state of excitement, pharyngeal distress or laryngospasm.

Such is the typical picture of the course of events after the intravenous administration of sodium amytal, irrespective as to whether the dosage is sufficient to produce complete analgesia or not.

Our patients as a rule have recovered or awakened from sodium amytal without restlessness. In only a few cases has it been necessary to give more than the usual postoperative injection of a sixth of a grain of morphine. The amytal apparently seems to work just as well without the preliminary morphine but we feel that the analgesic properties are enhanced by a preliminary injection of a sixth of a grain of morphine fifteen to twenty minutes before the expected time of operation.

Table 1

Name	Sex	Chart No.	Weight	Age	Surgery	Amytal Amt. Administered (Gram)	Time for Complete Unconsciousness (Minutes)	Analgesia	Supplemental Anesthesia	Recovery	Comment
G. W.	F.	53621	141	19	Thyroidectomy Graves' disease	1.0	7	...	Ethylene	Quiet	B.M. + 48
I. G.	M.	50848	112	54	Gastroenterostomy	1.0	5.5	+	.....	Quiet	
C. Z. S.	M.	51136	149	48	Cholecystectomy Appendectomy	1.0	6.5	+	Ether*	Quiet	
F. S.	M.	51559	126	18	Thyroidectomy Graves' disease	1.0	6	...	Ethylene	Restless	B.M. + 71
S. S.	F.	51639	128	27	Thyroidectomy Graves' disease	1.0	6	...	Ethylene	Restless	B.M. + 58
H. G.	F.	51648	100	33	Thyroidectomy Adenoma—hyperthyroidism	1.0	6.5	...	Ethylene	Quiet	B.M. + 38
S. T.	F.	52074	118	65	Thyroidectomy Carcinoma of thyroid	1.2	2	+	.....	Quiet	B.M. + 28
S. P.	F.	52587	114	18	Thyroidectomy Graves' disease	0.8	4.5	...	Ethylene	Quiet	B.M. + 58
A. P.	M.	52601	119	21	Thyroidectomy Graves' disease	1.0	8	...	Ethylene	Quiet	B.M. + 68
G. S.	M.	53158	128	41	Thyroidectomy	1.0	...	...	Ethylene	Restless	B.M. + 68
H. B.	F.	53148	94	21	Thyroidectomy Graves' disease	0.9	6	...	Ethylene	Quiet	B.M. + 68
E. S.	F.	53804	39	39	Thyroidectomy Adenoma of thyroid	1.0	6	...	Ethylene	Quiet	Congenital heart disease
T. G.	F.	53887	140	38	Thyroidectomy Adenoma of thyroid	1.0	8	+	Ethylene*	Restless	B.M. + 30
C. McK.	F.	54079	100	65	Thyroidectomy Adenoma of thyroid	0.8	5	...	Ethylene	Quiet	Asthenia
E. D.	F.	54055	116	40	Cholecystectomy Appendectomy	0.9	4.5	...	Ethylene*	Quiet	Pulmonary tuberculosis
J. W.	M.	54307	109	46	Thyroidectomy Graves' disease	1.0	6	...	Ethylene	Quiet	B.M. + 48
F. V.	F.	54292	82	16	Thyroidectomy Graves' Disease	0.9	8	+	Ethylene*	Quiet	B.M. +
E. H.	F.	54396	112	43	Laparotomy Perineorrhaphy	0.7	4	+	.....	Quiet	
E. F.	F.	54299	114	52	Thyroidectomy Adenoma of thyroid	0.9	5	+	Ethylene*	Quiet	B.M. +
W. D.	M.	54588	156	42	Herniotomy	0.7	6	...	Nitrous oxide	Quiet	
F. S.†	M.	54249	126	18	Thyroid crisis of Graves' disease No surgery	0.8	6	Slept 10 hours	.....	Quiet	Complete relaxation and rest obtained

* Supplemental anesthesia only necessary at beginning or end of operation.
† Used to produce unconsciousness in a patient verging on thyroidal delirium.

to promote rest, preoperatively, in highly toxic goiter cases, (8) in any condition where it is desirable to produce complete unconsciousness and restful sleep for six to twelve hours.

Since the preparation of this paper 25 additional cases of the same general character have been operated upon under intravenous sodium amytal.

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A NEW CYSTOSCOPE CORD*

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MILWAUKEE, WIS.

MAX NITZE in 1879 presented to the profession a cystoscope which has been modified by Brenner, Brown, Albarran, Lewis, Kollman, Kelly, Cullen, Buerger, Braasch, McCarthy, Young and others. With the improvement of the instrument and the technic in its use, urology has become an exact science.

During the past five years, while studying the bacteriology of the upper urinary tract, I have found it impossible to use a technic that was aseptic and practical, there being a constant danger of breaking the technic from the use of a cord that could not be boiled or sterilized in an antiseptic solution. With a desire to rectify the source of danger, I requested the American Cystoscope Makers, Inc. to make a cystoscope cord that could be boiled or sterilized in chemical solutions.

Through the cooperation of W. H. Dodge and C. C. Steffek, the following cord was made (Fig. 1).

The rubber composition of the cord is such that it is made to withstand the various chemical actions during sterilization and the electrical contact is heavily insulated with vulcanized rubber with an on-and-off switch at contact to eliminate the possible corrosion at the switch.

This cord has been used routinely for the past two months, being sterilized by boiling or in mercuric iodide solution, with all control cultures being negative.

FIG. 1.

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PHARMACOLOGICAL ACTION OF SODIUM AMYTAL;

INCLUDING A STUDY OF ITS EFFECTS UPON RESPIRATION AND CIRCULATION IN RELATION TO LOCAL, REGIONAL, AND GENERAL ANESTHESIA*

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A GENERAL experimental and clinical discussion of the pharmacological action of sodium amytal may be conveniently divided into three parts, with further subdivision as follows:

I. General Pharmacological Actions.
   1. Metabolism
   2. Central Nervous System and Smooth Muscle
   3. Circulatory System
   4. Respiratory System

II. The Effects of Sodium Amytal in Relation to Untoward Reactions Following the Use of Local Anesthetics.

III. The Minute Volume of Respiration; Blood Pressure and Pulse. Effects of Combinations of Sodium Amytal, Morphine, Scopolamine, Ether and Carbon Dioxide.

I. GENERAL PHARMACOLOGICAL ACTIONS

Effects on Metabolism. Amytal was introduced by Page[1] in 1923 as a laboratory anesthetic. He stated that it was capable of maintaining satisfactory anesthesia without producing hyperglycemia. Also, that its action was unaccompanied by associated generalized inhibition of carbohydrate metabolism as indicated by the fact that hyperglycemia was obtained under amytal anesthesia upon splanchnic stimulation or severe hemorrhage, and insulin still produced hypoglycemia unaccompanied by convulsions. Hepburn, Latchford, McCormick, and Macleod,[2] Britton,[3] Markowitz,[4] and Collens,[5] have found normal or slightly subnormal values for blood sugar after amytal administration. Deuel, Chambers and Milhorat,[6] also observed that after intraperitoneal injection of amytal in doses of 50 to 75 mg. for each kilogram of weight in normal fasting dogs, no change in blood sugar level occurred in periods as long as six to eight hours after injection. However, Weiss[7] reported that amytal anesthesia in cats induced an increase in the blood sugar level of 100 to 250 per cent above the fasting level, and in dogs, one of 80 to 150 per cent. The maximal values of the blood sugars were obtained one to two hours after the injection of the amytal, and the hyperglycemia persisted from six to twenty hours. Underhill and Sprunt[8] found that in a series of 10 experiments on rabbits, 8 gave evidence of distinct hyperglycemia, which usually appeared within an hour, or somewhat later, and in some cases lasted for several hours. These results followed doses ranging from 50 to 100 mg. for each kilogram, of amytal, whether given by mouth, subcutaneously or intraperitoneally. Hines, Boyd and Leese,[9] in 1926, stated that amytal anesthesia lessened the ability of an animal to handle glucose when injected by the continuous intravenous method. This was indicated by increased hyperglycemia and glycosuria, associated with slight lowering of the plasma pH. A comparison of glycogen formation in the unanesthetized and anesthetized (amytal) animal was made in experiments on dogs by Hines, Leese and Barer,[10] in 1928. It was found that approximately the same increase in muscle glycogen occurred in animals with or without amytal anesthesia. However, the increase in liver glycogen was over twice as great in the unanesthetized animal as in the experiments in which the glucose injections were made under amytal anesthesia.

Metabolic changes in patients after sodium amytal anesthesia were reported

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Zerfas and McCallum[11] measured the effects of sodium amytal on uterine contractions of patients in labor by the use of a mercury manometer which was connected to a Voorhees bag inserted into the cervix. In this manner the contractions were recorded. Doses up to 0.018 gm. or one-third grain for each kilogram were given within two hours without affecting the force, duration or frequency of uterine contractions.

Judging from the actions of barbituric acid derivatives closely related to sodium amytal, one would infer that these compounds were without marked action upon smooth muscle. Thus Jackson[17] in 1922, showed that isopropylethyl barbituric acid did not cause broncho-constriction in dogs so far as its direct action on the bronchioles was concerned. He also stated that the stomach and intestines were almost entirely uninfluenced by ordinary doses of this compound.

The Circulatory System. A careful study of the pharmacological actions of isopropylethyl barbituric acid was made by Jackson[17] in 1922. One cannot assume that the actions of closely related barbituric acid derivatives are identical, but it is safe to conclude that they are analagous and comparable to a certain degree. Writing on isopropylethyl barbituric acid, Jackson pointed out that with small doses, the blood pressure showed a slight fall that was both insignificant and temporary. The heart beat was but little affected by the drug when therapeutic doses were injected suddenly directly into the circulation. He concluded that the heart was entirely outside the sphere of action of the drug when given in any such quantities as would be used medicinally. The vagus inhibitory mechanism was entirely unaffected by the drug.

In experiments on dogs, rabbits and cats, Lieb and Mulinos,[18] 1929, found a temporary (one and one-half to two hours) paralysis of the vagus inhibitory mechanism of the heart, as a result of the administration of isoamylethyl barbituric acid. Edwards and Page,[19] in 1924, showed that experimentally, sodium amytal was without effect on the circulatory system, a well-sustained blood pressure with little change in the heart rate, and no alteration in dynamic capacity of the heart being noted. According to Drabkin and Edwards,[20] this hypnotic is without effect on blood concentration.

The coronary circulation was studied by Gruber and Roberts,[21] in 1926. All the barbituric acid derivatives tested, including barbital, luminal, sodium luminal, amytal and somnifene, in dilute solutions, produced coronary vasodilatation when introduced into the perfusion fluid of an isolated cat or rabbit heart. Concentrated solutions produced variable results, but these were believed to be due in part, if not wholly, to the change in the pH of the perfusion fluid.

Many observations on patients have been made by Zerfas and McCallum.[13] They noted a variable response in the pulse rate during and shortly after the completion of the injections of sodium amytal. Usually the rate was increased; it was very seldom decreased, and often was unchanged from normal. The blood pressure practically always decreased during the time of injection, but usually returned to its previous level within a few minutes. These observations have been quite generally confirmed, as is indicated by the report of Mason and Baker.[12] In their patients the pulse rate, if elevated by emotional excitement, was reduced during the induction of anesthesia. In all other cases, however, the pulse appreciably quickened after injection of the sodium amytal, an average of + 15 beats per minute. The blood pressure, in all but a few instances fell, the systolic an average of 30 mm. of mercury, and the diastolic an average of 15 mm., during the induction of anesthesia, but returned to the normal level early in the operation or else was restored to normal by the administration of ephedrine.

The moderate acceleration of the pulse described is probably due, in part, to

temporary vagus inhibition. The fall in blood pressure appears to be anaphylactoid in origin, in common with the circulatory response seen after intravenous injection of solutions of many drugs. It has been our observation that the more dilute the sodium amytal solutions and the more slowly it is injected, the less apparent are the vasodilator effects.

The Respiratory System. Attention is again called to the work of Jackson[17] on the analagous barbituric acid derivative, isopropylethyl barbituric acid. He stated that with moderate doses the respiration and circulation appeared to be practically uninfluenced by the drug. After very large doses, a considerable increase in the depth of respiration was seen, as the respiration became progressively slower. Respiratory depression became more and more evident with increasing doses, and was the final cause of death in fatal cases. With care, the animal could be repeatedly revived after the respiration ceased, thus showing that artificial respiration was the chief remedy needed in case of severe poisoning with the drug. Jackson observed that it was often very advantageous in experimental work to give one or two fairly large injections of the isopropylethyl barbituric acid, to quiet an animal which did not take ether well, but continued to breathe rapidly and irregularly, and to have slight convulsive seizures, but in which a slight excess of ether tended to stop the respiration or greatly lower the blood pressure. In such animals, the reflexes could be quieted and the animal reduced to a calm and satisfactory condition, by two or three fair-sized injections of the drug. The ether could then be continued without further difficulty.

In 1926, Page and Coryllos[22] described the effects of sodium amytal on the respiration as follows:

> In general, the respiration is decreased in rate, and slightly, in amplitude, with increasing dosage. Just before death the rate increases, and certain irregularities are at times observed in the animals under very deep anesthesia. It is not uncommon to find a series of three respiratory movements alternating with prolonged pauses. That the respiratory center is still responsive, may be demonstrated by pressure on the thorax producing the suffocation reflex. Such a procedure immediately increases the rate of respiration two to threefold.

They recommended for dogs, a dosage of 45–60 mg. for each kilogram as being most suitable for ordinary experimental procedures. With this optimum dosage, they found the circulation and respiration well maintained over a wide range of surgical procedures.

Clinical descriptions of the respiratory changes, following intravenous injections of sodium amytal, have been reported by Zerfas and McCallum.[13] They stated that the respirations following loss of consciousness, were usually decreased in amplitude, were regular, and were more apt to be slightly increased in rate, though frequently they remained normal. There was little change in the color of the skin, although occasionally a slight degree of cyanosis was present. In a few patients, considerable blanching of the skin occurred. In the majority of instances, however, the color of the skin remained unchanged. When ether, nitrous oxide and oxygen, ethylene, or a mixture of carbon dioxide and oxygen were given, both the amplitude and rate of respiration increased.

Mason and Baker[12] observed the respiration to become shallow, with a slight increase in the rate. In a few cases, the respiratory rate, however, fell as low as 12 per minute. The color in all but a few cases remained uniformly good. In all their surgical cases, morphine sulphate $\frac{1}{16}$ to $\frac{1}{4}$ grain with atropine sulphate $\frac{1}{150}$ grain was given one hour prior to the administration of the sodium amytal.

II. THE EFFECTS OF SODIUM AMYTAL AND ARTIFICIAL RESPIRATION IN EXPERIMENTAL NOVOCAINE POISONING

Since the introduction of cocaine into surgical practice as an anesthetic, many

instances of toxic action of the drug have been observed. Accordingly, numerous substitutes for cocaine have appeared with the idea of avoiding the undesirable effects of local anesthetics. As a substitute for cocaine, novocaine or procaine has found the most extensive use.

Other approaches to the problem are being made. More attention is being given to the doses of the local anesthetics administered, and particularly to the concentrations of the solutions used. Furthermore, the method and speed of injection, and the temperature of the solutions have come to be recognized as factors of great importance. Nevertheless, in many instances, careful attention to the details of administration of the local anesthetics does not eliminate entirely the possibility of objectionable reaction.

Experience has demonstrated that novocaine is less toxic than cocaine, only when certain conditions prevail. According to Eggleston and Hatcher,[23] 1916:

> One is not justified in speaking of ratio of toxicity of novocaine and cocaine, without reference to the mode and rate of administration, the concentration of the solution used, and the species of animal employed. Novocaine is safer than cocaine only when it is used properly, special attention being given to the heart and respiration, and avoidance of rapid entrance of the drug into the circulation.

More recently Lundy,[24] in 1927, and McCuskey[25], in 1928, have presented an abundance of clinical evidence in accord with the opinions of Hatcher and Eggleston

Further investigation of the origin of the untoward reactions seen clinically following cocaine and novocaine injections would seem to be important. Consideration also should be given to the possibility of counteracting and preventing the ill effects of local anesthetics by the use of other drugs and procedures, which have an antagonistic action.

Prevention of convulsions and the fatal result of ordinarily lethal doses of cocaine by the use of barbital, was described by Hofvendahl,[26] in 1921. An important series of results was obtained by Tatum, Atkinson and Collins,[27] in 1925. They were able to increase the tolerance of animals to cocaine by the use of artificial respiration, but more particularly by the administration of barbital combined with paraldehyde. The convulsions seen in cocaine poisoning appeared to be especially detrimental. The survival of the animal often appeared to depend upon their severity and duration. Barbital and paraldehyde were shown to be highly effective in removing those convulsions. Knoefel, Herwick and Loevenhart,[28] 1928, stated that sodium amytal was much more efficient than barbital in preventing fatal outcome from cocaine injections in rabbits. Magnesium sulphate, on the other hand, though a powerful depressant, rendered animals much more suceptible to novocaine and cocaine.

Following these observations, clinical reports appeared, indicating the possible value of the barbiturates as preventives of untoward reactions due to local anesthetics. Leshure,[29] 1927, reported that while morphine alone, or combined with scopolamine, did not prevent the occasional toxic reactions due to local anesthetics, from 0.4 to 0.8 gm. of sodium veronal administered by mouth routinely before operative procedures with a local anesthetic, was efficient to prevent toxic reactions.

Williams,[30] 1927, used 0.3 gm. of barbital two hours and one hour before the beginning of operations with local anesthetics. He also noted beneficial results. It was observed by Martin,[31] 1928, that the frequence and severity of toxic reactions due to novocaine were considerably reduced in patients receiving 0.60 gm. of barbital the night before, and one hour before the surgical operation. Also, Guttman,[32] 1928, stated that the routine hypodermic administration of from 0.18 to 0.3 gm. of barbital, reduced the frequency of toxic reactions following the use of novocaine. Lundy,[33] 1929, reported that preliminary medication with sodium

amytal, in most instances combined with small doses of morphine, established a good mental attitude in the patient toward local anesthesia. No convulsions appeared, nor was operation postponed in any instance because of nausea and vomiting. He felt that the barbiturate protected the patients against untoward effects of unintentional intravenous injection of novocaine, in addition to producing hypnosis.

At the suggestion of Dr. Lundy and Dr. Rowntree, an experimental and clinical study of the nature and extent of the antagonism existing between the actions of novocaine and sodium amytal was made by Dr. Lundy and myself at the Mayo Clinic.

It was observed that novocaine in overdoses in patients was succeeded by the following phenomena: fall in blood pressure, usually a slow pulse, shallow breathing, pallor and cyanosis, sweating, sometimes nausea and vomiting, and occasionally mental confusion and apprehension. In one or two instances, convulsions, preceded by great anxiety and followed by depression, had been observed. Many of the same effects of the novocaine were evident in the experiments on dogs which follow:

Method. Local or spinal anesthesia was used to prepare dogs for records of respiration from the trachea, and of blood pressure from the femoral artery. The respiration was recorded by means of a membrane manometer, and the blood pressure by the use of a mercury manometer. Twelve major experiments were performed.

Results. 1. After a definitely hypnotic dose of the sodium salt of isoamylethyl barbituric acid had been administered, novocaine injected intravenously in repeated doses of a 20 per cent solution, and averaging about 200 mg. for each animal at each injection, produced its characteristic fall in blood pressure accompanied by decline in rate and depth of breathing. The presence of the sodium amytal did not seem to intensify the effects of novocaine observed in control experiments without the preliminary administration of the amytal. (Graphs No. 3 and 4.)

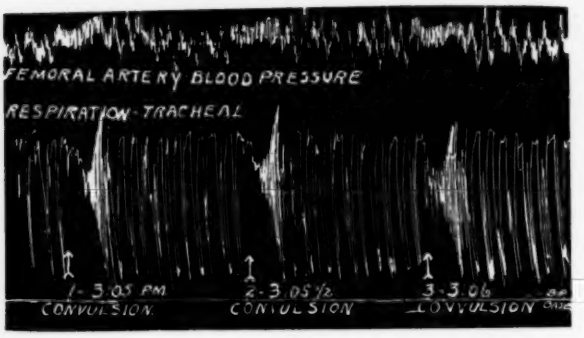
2. After isoamylethyl barbituric acid had been administered, convulsions did not appear when novocaine was administered intravenously, either by slow injection of a 1 per cent solution, or by injection of the animal with repeated doses of 20 per cent solution, each dose of which contained 200 mg. of novocaine. (Graphs No. 2, 3, and 4.)

3. The fall in blood pressure in animals, after adequate doses of novocaine had been given intravenously, closely paralleled and coincided with the respiratory depression. (Graphs 3 and 4.)

4. After complete respiratory paralysis had resulted from the intravenous administration of novocaine, the circulatory system almost always maintained its functions, though depressed, without support of circulatory stimulants for long periods. During this interval, adequate and properly administered artificial respiration was given. This period was characterized in the majority of cases, by prompt recovery in the level of the blood pressure, and usually later by recovery of the function of respiration. Respiratory paralysis from injections of novocaine into the spinal fluid responded equally well to mechanical ventilation. In one experiment of this type, the respiration was paralyzed completely for ten hours by a large intraspinal injection of novocaine. Mechanical ventilation alone was adequate to sustain the animal until recovery, with only a slightly subnormal blood pressure. This animal's spinal cord later showed marked evidence of degeneration as a result of the highly concentrated and excessive amount of novocaine. Twenty-five hundred milligrams of the drug in 50 per cent solution were introduced into the lumbar region of the spinal canal. (Graphs 3 and 4.)

5. In several instances, impairment or paralysis of the intercostal muscles, with the diaphragm still functioning well, following the administration of novocaine, intra-

venously or intraspinally, was accompanied by a low blood pressure. Artificial respiration applied to these animals resulted in

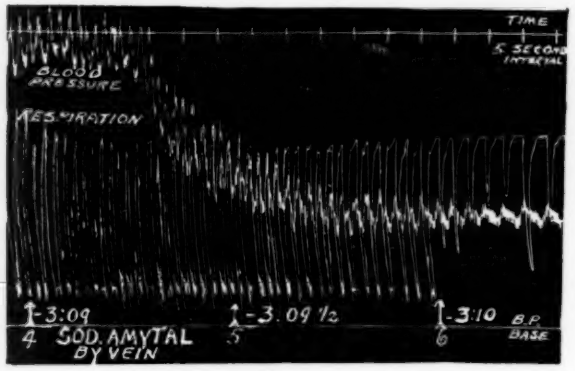


GRAPH 1. Dog No. 1. Wt. 11.75 kg. 9–27–28.

Anesthesia:		Quinine urea hydrochloride 0.5 c.c. of 50 per cent, spinal. One-half per cent novocaine local for introduction of tracheal cannula.
2:55 P.M.		50 c.c. of 1 per cent novocaine by continuous intravenous injection, 20 c.c. per minute.
3:00		17 c.c. of 1 per cent novocaine continuous intravenous injection, 20 c.c. per minute.
3:05	(1)	Convulsion.
3:05½	(2)	Convulsion.
3:06	(3)	Convulsion.

distinct elevation of the blood pressure to the control level.

6. Convulsions were induced in animals by slow intravenous injection of 1 per cent novocaine. The sodium salt of isoamylethyl barbituric acid, given intravenously, stopped the convulsions immediately and rendered the animals stuporous and relaxed. There was considerable drop in blood pressure accompanied by impaired respiration for from ten to twenty minutes after large intravenous doses of sodium amytal had been given in the presence of convulsions caused by novocaine. During the convulsions there was a definite spastic paralysis of respiration, in the expiratory position, with each seizure. The blood pressure declined rapidly after the convulsions became frequent, intense and prolonged, and the respiratory exchange became definitely incomplete. After prolonged and frequent convulsions exhaustion appeared rapidly, respiration ceased and the blood pressure fell abruptly. At this time artificial respiration seemed to be lacking in supporting effect, although it had been effective in those animals in which respiratory paralysis had been produced by novocaine, but in which convul-



GRAPH 2. Dog No. 1. 9–27–28.

3:09 to 3:09½	(4 to 5)	Injection by vein of 3.6 c.c. of 10 per cent sodium amytal. (Total of 360 mg. or 30 mg. per kilo).
3:10	(6)	Definite fall in blood pressure to horizontal level. Definite slowing of respiratory rate and decrease in amplitude.

sions had been prevented by the use of sodium amytal. (Graphs 1, 2, 3, and 4.)

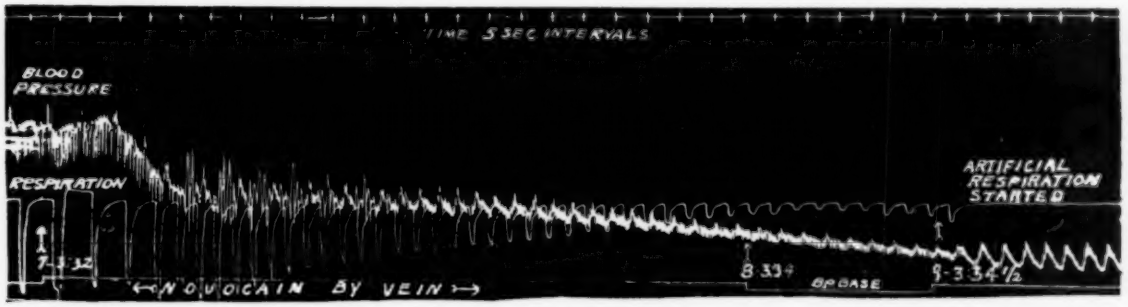
Discussion. These results place additional emphasis on the respiratory factor in depression from local anesthetics, and the close correlation between circulatory and respiratory depression, after toxic doses of novocaine were given intravenously to dogs, suggests a causal relationship between the two phenomena. (Graph 3.) This is also indicated by the pressor effect often seen when adequate ventilation is provided in the presence of novocaine depression. (Graphs 3 and 4.)

Similarly, oxygen administration and artificial respiration applied to animals and patients, in the presence of low blood pressure and diaphragmatic breathing after intraspinal novocaine, as described in section five of the results, have been observed to be of definite value in raising the blood pressure. The beneficial effect here may be due to relief of existing anoxemia as a result of incomplete pulmonary ventilation, or may provide additional mechanical assistance to the return flow of blood to the heart.

In view of the need for adequate pulmo-

nary ventilation in novocaine poisoning, the value of the barbiturates in controlling the convulsions is enhanced.

fall in blood pressure, with a closely paralleled depression in respiration, ending in respiratory paralysis. Hence, at (9) the



Graph 3. Dog No. 1. 9–27–28.

3:32 to 3:34 (7 to 8) Injection by vein of 30 c.c. of 1 per cent novocaine.
3:34½ (9) Artificial respiration started.

Discussion of Graph 1: The convulsions shown are three of a series of ten produced in the animal by the intravenous novocaine. Note the rapid, deep respiration with fixation of the chest in the expiratory position during the spasms. The convulsions were very violent and were recurring at half-minute intervals. The blood pressure had not begun to decline. The animal was in a marked stage of mental and motor excitement.

Discussion of Graph 2: The injection of sodium amytal here was probably unnecessarily rapid, and the dose was no doubt more than would have been required. The almost immediate change from a state of motor and mental excitement of the animal, with extreme tachypnea and hyperpnea, to a condition of stupor and complete relaxation was very impressive. The respiration became regular, rhythmical and appeared to be approximately normal. No convulsions or spasms appeared after the amytal injection.

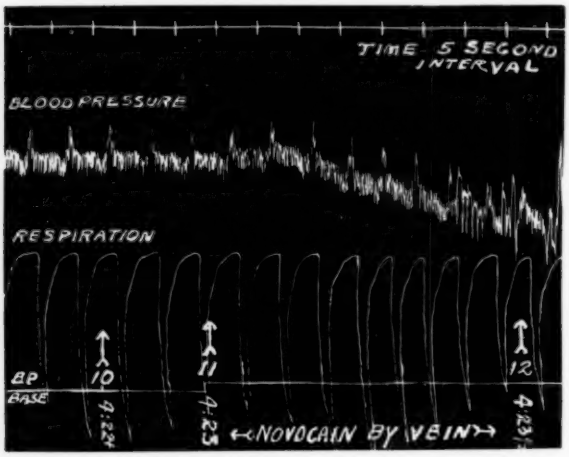
Discussion of Graph 3: In a relatively short time, twenty minutes, the blood pressure increased from the low level of 65 in Graph 2, to 90, seen at (7) in Graph 3. At this time, although the rate of respiration was about 10–12 per minute, it was of good amplitude. At this point the further injection of 1 per cent novocaine intravenously caused a progressive respiration machine was started. It was connected directly with the tracheal cannula, and supplied alternate positive and negative air pressure, with safety valves to insure against excessive pressure changes within the lung. The valves were so arranged that air was taken from the room, introduced into the lungs, and withdrawn and discharged into the room again. The ventilator consisted of a motor driven bellows with adjustable speed and air pressure.

Discussion of Graph 4: Here it is seen that within forty-five minutes after a series of 10 violent convulsions due to novocaine, an unnecessarily large dose of sodium amytal intravenously, and a total of almost 1 gm. of novocaine intravenously, the blood pressure is 110, within the normal range, and there is an efficient respiration.

Conclusions 1. Despite the criticism of mechanical methods of artificial respiration, by the proper use of adequate artificial ventilation, life can be sustained in most animals which would otherwise succumb to overdoses of novocaine, given by vein or introduced into the spinal canal.

2. Isoamylethyl barbituric acid offers protection against convulsions caused by novocaine. If convulsions are in progress, due to novocaine, this drug or some other safe, soluble barbiturate, is the treatment of choice.

3. Although the isoamylethyl barbituric acid in proper doses will protect against convulsions caused by novocaine,



GRAPH 4. Dog No. 1. 9–27–28.

4:22 plus. (10) Blood pressure back to 110. Efficient respiration.

4:23 (11) Injection of 1 per cent novocaine by vein, started.

4:23½ (12) Definite effect on the respiration, decreased rate and depth, with gradual fall in blood pressure.

it will not prevent the depression brought about by overwhelming doses of the local anesthetic.

4. The combination of isoamylethyl barbituric acid or another safe, soluble barbituric acid hypnotic, with properly controlled artificial respiration, offers the greatest hope for saving of life in cases of severe poisoning by novocaine.

III. MINUTE VOLUME OF RESPIRATION; BLOOD PRESSURE AND PULSE, EFFECTS OF COMBINATIONS OF SODIUM AMYTAL, MORPHINE, SCOPOLAMINE, ETHER, AND CARBON DIOXIDE

Shonle and Moment,[35] 1923, Dox and Hjort,[36] 1927, and Eddy,[37] 1928, have published results of experiments which indicate that sodium isoamylethyl barbituric acid should be classed among the most effective hypnotics of the barbituric acid series.

Zerfas and McCallum,[13] Lundy[33] and others, have emphasized the value of sodium amytal as a basal narcotic for general and local anesthesia. For this purpose it is important to know the actions of the drug, particularly upon the functions of respiration and circulation, both alone and in combination with other narcotic drugs, commonly employed in anesthetic work. Detailed studies of the action of the barbiturates on respiration, particularly, have been rather limited. Bouckaert,[38] 1926, reported the effects on the respiration of somnifene, a mixture of diethyl barbituric acid and allylisopropyl barbituric acid. In doses of 0.2 to 0.4 c.c. for each kilogram of body weight in a rabbit, it caused deep narcosis, greatly reduced the output of carbon dioxide, and diminished the depth and frequency of respiration. Others have emphasized the depressing effect on respiration of large doses of hypnotics derived from barbituric acid both in patients and in experiments on animals.

In this investigation, therefore, special attention has been given to respiration. Data was collected on the blood pressure and pulse rate, largely for the purpose of correlation.

I conducted the experiments with the idea of obtaining evidence as to the effects of preliminary medication on the safety and efficiency factors of anesthesia. The state of the respiration during the narcosis, and its response to stimulation by carbon dioxide was used as the main index to the degree of reduction of vital reserve of the animal. An attempt was made to correlate this information with the degree of hypnosis, analgesia, or anesthesia produced.

Method. Clinical methods were employed. The minute volume of respiration was determined by the use of a one-way breathing system, including delicate intake and exhaust valves, an intake bag, and a dry gas meter to measure the flow of air into the breathing bag. An air-tight mask connected the system to the animal. The dose of carbon dioxide was measured and maintained constant at 500 c.c. for each

minute by the use of a Foregger metric gas machine. Rebreathing and obstruction were carefully avoided.

Systolic blood pressure was determined by the auscultatory arm-cuff method, and heart rate by precordial palpation.

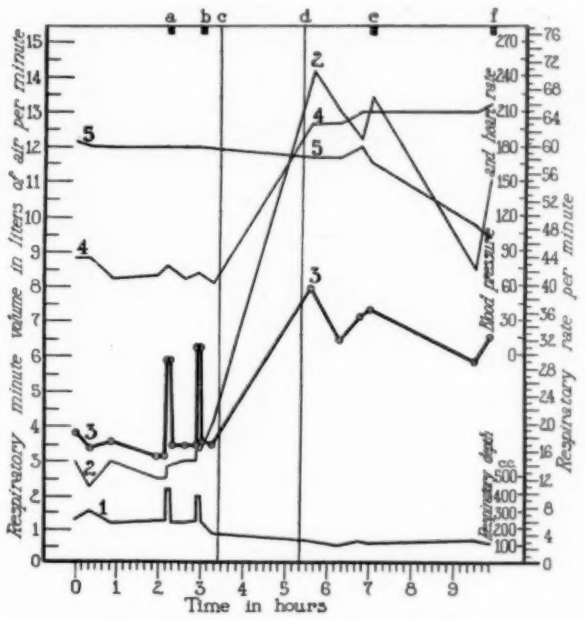
As far as possible the same animal was used for successive experiments to avoid the effect of individual variation. Stimulating and depressing effects of operative procedure were entirely eliminated in this series of experiments.

Doses that corresponded to therapeutic amounts in man were administered. Morphine sulphate was given in the proportion of 4 mg. for each kilogram of body weight hypodermically. Sodium isoamylethyl barbituric acid was given in the proportion of 20 mg. for each kilogram of body weight intravenously, in a 10 per cent solution, at the rate of 1 c.c. for each minute. The dosage was kept constant in succeeding experiments of related character.

Results. Atropine and Ether (Graph 5). The control minute volume of respiration over a period of two hours is seen to range between 3 and 4 liters per minute (curve 3). At (a) and (b), control measurements of response of the respiratory mechanism to carbon dioxide were made. At (c), $\frac{1}{100}$ grain of atropine sulphate was given to assist in the control of excessive mucus. The next one and one-half hours were devoted to establishing deep ether anesthesia in the animal.

Deep etherization was accomplished at (d) and was accompanied by the following changes: the rate of respiration (2) increased rapidly to 68. With this high rate of respiration there occurred considerable reduction in the depth (1). As a result of these changes the minute volume (3) was increased to twice the normal value. The breathing became largely diaphragmatic in character. Carbon dioxide in control dosage (e) increased the rate of breathing slightly but decreased the depth during the deep etherization. It had little effect on the minute volume.

Later at (f), when the ether concentration was lessened to that of a moderate depth of anesthesia, characterized by combined thoracic and diaphragmatic



Graph 5. Dog No. 2. 13.4 kg. 11–18–29.

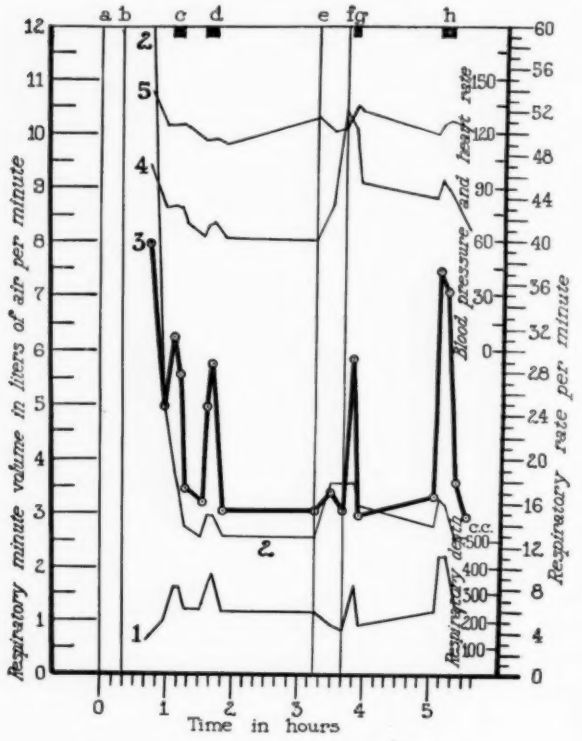
1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg. a, b, e, and f, each 500 c.c. CO_2 per minute in air (five-minute periods).
c. Atropine sulphate $\frac{1}{100}$ grain hypodermically.
d. State of deep ether anesthesia.
f. Moderate degree of ether anesthesia.

breathing, the control dose of carbon dioxide resulted in a slight increase in the rate of respiration, and in the minute volume.

Two hours of deep etherization were accompanied by a definite fall in systolic blood pressure (5) and a marked acceleration in pulse (4).

Comment. It is evident that the rapid shallow breathing of deep etherization resulted in an increase in the minute volume. However, rapid shallow breathing is considered to be a relatively inefficient type of respiration. Furthermore, the absence of thoracic excursions might result in inadequate pulmonary ventilation and in imperfect return of blood to the heart

leading to anoxemia. At this stage it is possible for the central depression of the respiratory mechanism, as a result of prolonged deep etherization, to render the use of other than small doses of carbon dioxide inadvisable. It has been my experience to observe sudden respiratory paralysis and death in a deeply etherized dog from the use of amounts of carbon dioxide that had formerly been only a stimulating dose.


a b c d e f g h
Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory depth c.c.
Respiratory rate per minute
Time in hours

Graph 6. Dog No. 3. 17.2 kg. 9–30–29.

1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.

a. Sodium amytal 450 mg., 10 per cent solution by vein, 1 c.c. per minute.
b. Morphine sulphate 1 gr. hypodermically.
c., d., g., h. CO_2, 500 c.c. per minute in air.
e. to f. Twenty-five minutes of moderate etherization to production of complete anesthesia.

Lemon's experiments[39] point to the fact that the respiratory reserve of animals deprived of intercostal breathing, and of the activity of a portion of their diaphragms, is lessened when they are subjected to etherization. His animals, prepared by nerve section, could meet the respiratory demands of rather active exertion while awake. They required artificial respiration to sustain life when they were anesthetized with ether.

One might inquire, therefore, as to the true margin of safety remaining after full relaxation has been obtained with ether alone. It would seem that long periods of deep etherization might often dangerously restrict the vital reserve of the animal or patient.

Morphine, Sodium Isoamyletbyl Barbituric Acid, and Etber (*Graph* 6). The animal was given a moderate dose of sodium amytal at (a), followed by a small dose of morphine at (b). Profound hypnosis with analgesia developed rather slowly and was not accompanied by full anesthesia with relaxation. Pulmonary ventilation, as indicated by the minute volume, (3), corresponded to that of an animal when at rest, and a high degree of irritability of the respiratory center to carbon dioxide remained. Attention is called to the horizontal level of the minute volume curve between (d) and (e). At (e), full etherization was added and was continued for twenty-five minutes. It was characterized by complete anesthesia and muscular relaxation accompanied by delayed thoracic breathing. Another test with carbon dioxide at this time (g) showed a response equal to that obtained before etherization. Slight acceleration of the rate of respiration with a corresponding reduction in the depth and an increase in the pulse rate accompanied the administration of the ether (e) to (f).

Recovery from the combined effects of morphine, sodium amytal and ether, was rapid and complete. This is indicated by marked improvement in minute volume of respiration seen at (h) as a result of the standard dose of carbon dioxide.

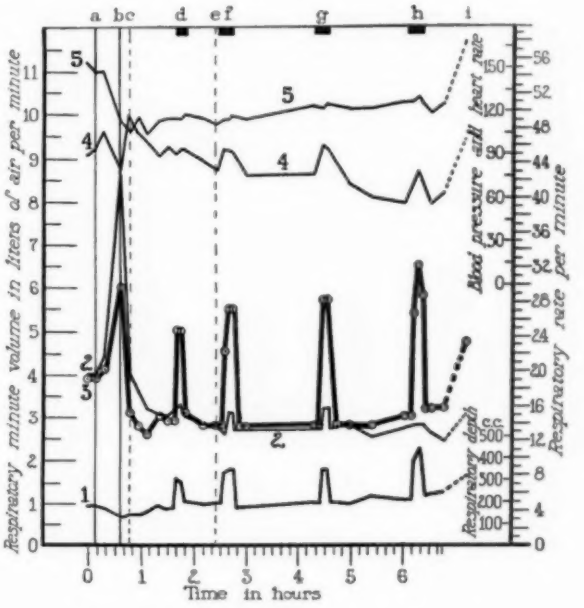
At no time during the experiment was overstimulation or depression apparent in the animal, and the uniform course of events was in sharp contrast to the uneven

and irregular responses of animal No. 2, under the effects of ether alone.

Comment. With a suitable combination and sequence of morphine, sodium amytal and a general anesthetic, such as ether, full surgical anesthesia with relaxation was safely and easily established and adjusted. At the same time there appeared to be retained what may be judged to be a definitely higher degree of respiratory reserve than when ether alone, or ether preceded by morphine alone, was used to a state of similar degree of anesthesia and relaxation.

Other advantages of the preliminary medication are as follows: small doses of morphine followed by moderate doses of sodium amytal produced unconsciousness and analgesia in the animals in a manner in every way analogous to the onset of normal sleep. With the combination, this marked physiological effect can be induced in patients much more safely and effectively than can be accomplished with morphine alone, or even with morphine and scopolamine. At the same time, the small preliminary dose of morphine nearly always greatly reduces the amount of barbituric acid required, and renders its action more uniform, more prolonged and more intense. Both the morphine and the sodium amytal usually considerably reduce, in patients, the amount of general anesthetic necessary as well as the concentration required for complete anesthesia and relaxation. Again, the supplementary effect of the relatively small amount and low concentration of the inhalation anesthetic, or in some instances local anesthetic, minimize the morphine and sodium amytal requirements.

The effects of the inhalation or local anesthetic pass off quickly. The effects of morphine and sodium amytal continue and, with only small additional doses of morphine, at rather long intervals, suffice to control postoperative distress and restlessness. By the use of the morphine, sodium amytal and inhalation or local anesthetic, all in minimal amounts, respiratory quiet and impairment of respiratory reflexes, during and after operation, are reduced to the minimum.


a b c d e f g h i
Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory rate per minute
Respiratory depth
c.c.
Time in hours

Graph 7. Dog No. 4. 13.2 kg. 10–1–29.

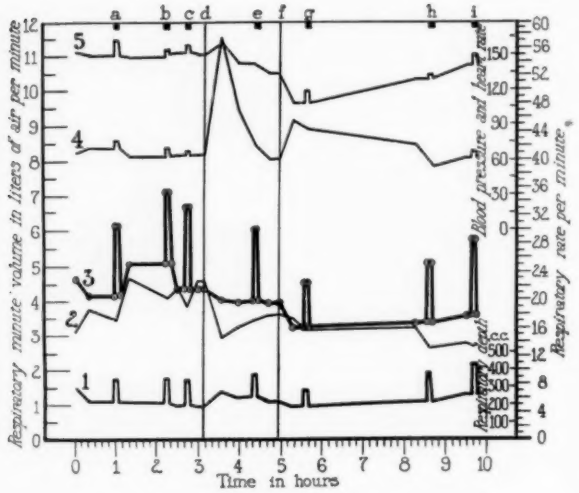
1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.
a. Morphine sulphate ¾ grain hypodermically.
b. Sodium amytal 260 mg., 10 per cent solution by vein 1 c.c. per minute.
c. to e. Complete anesthesia.
d., f., g., h. CO_2, 500 c.c. per minute in air.
i. Determination twelve hours later.

Finally, it is to be remembered that, owing to the presence of the barbiturate in the combination, there is complete amnesia for the anesthetic and surgical procedures, and to a large extent in many cases, for the postoperative discomforts.

Bumm's results which were published in 1927,[40] are of interest from the point of view of the use of the barbituric acid derivatives for basal narcosis in general anesthesia. He worked with pernocton which is sodium butylbetabrompropenyl barbituric acid, and recommended that it be used only as an hypnotic to be followed by the production of anesthesia with ether or chloroform. He considered this practice to be in no way dangerous,

and regarded it as a useful procedure in anesthetic work.

Considering the compounds of barbi-


a b c d e f g h i
Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory rate per minute
Respiratory depth c.c.
Time in hours

Graph 8. Dog No. 4. 14 kg. 11-13-29.

1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.

a., b., c., e., g., h., i. CO_2, 500 c.c. per minute in air.

d. Morphine sulphate ¾ grain and scopolamine hydrobromide 1/100 grain hypodermically.

f. Sodium amytal 260 mg., 10 per cent solution by vein, 1 c.c. per minute.

turic acid, therefore, as only an aid in the preparation of patients for full anesthesia by inhalation or local anesthetic agents, it was attempted in the later experiments to measure the effects of sodium amytal on the respiration when used alone, or in combination with morphine, or with morphine and scopolamine.

Morphine and Sodium Isoamylethyl Barbituric Acid (Graph 7). The morphine was given at (a), and was followed by marked increase in minute volume of respiration (3), due largely to an increase in the rate (2). There was a corresponding decrease in the depth of respiration as seen in curve (1). This result is quite the rule with dogs after morphine administration.

The sodium amytal was given at (b) and was followed very promptly at (c) by return of the minute volume to somewhat below normal, largely as a result of a decrease in rate of breathing. However, the combination did not result in a reduction of the minute volume of respiration which could be accurately described as a state of depression. It appeared to be rather a state of respiratory quiet, the decline in rate of breathing being compensated by an increase in depth. A good state of irritability of the respiratory center to the stimulating effect of carbon dioxide remained (d). It is noteworthy that these changes occurred in the presence of full anesthesia and marked relaxation lasting about one and one-half hours (c) to (e).

The maximal fall in minute volume was established within twenty to thirty minutes after the drugs had been administered. From this point on, there was gradual, but definite recovery approaching the normal level of minute volume and of irritability to carbon dioxide, (f) to (h).

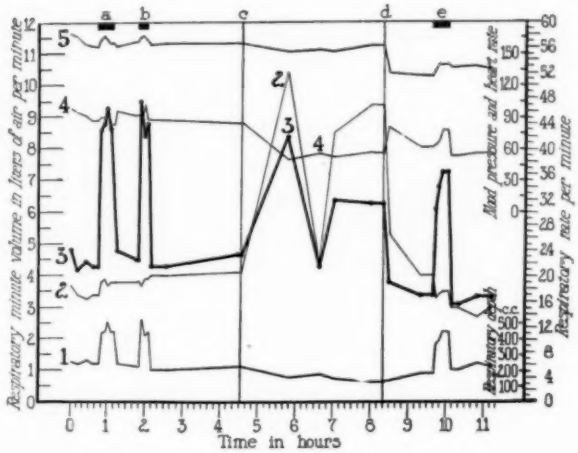
There was a progressive moderate decline in the pulse rate (4), with an initial fall in blood pressure and gradual recovery toward the control level.

Comment. The degree of reduction of minute volume as a result of administration of the morphine and sodium amytal sequence, was seen a number of times when the animal was lying quietly at rest, before any medication had been given. The type of respiration observed corresponded well with that described in dogs in normal sleep.

The rapidity with which the new level of pulmonary ventilation is established, after morphine followed by sodium amytal, facilitates estimation of the maximal reduction in minute volume of respiration which is likely to occur after the administration of these drugs in combination and sequence.

Morphine, Scopolamine, and Sodium Isoamylethyl Barbituric Acid (Graph 8). Control determinations of carbon dioxide irritability were made at (a), (b), and (c). At (d) the morphine and scopolamine were administered. The result of this combination was only a slight reduction in minute

volume and carbon dioxide irritability. There was a definite gradual decline in the blood pressure and a marked abrupt


a b c d e
Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory rate per minute
Respiratory depth c.c.
Time in hours

Graph 9. Dog No. 4. 13.7 kg. 10–18–29.

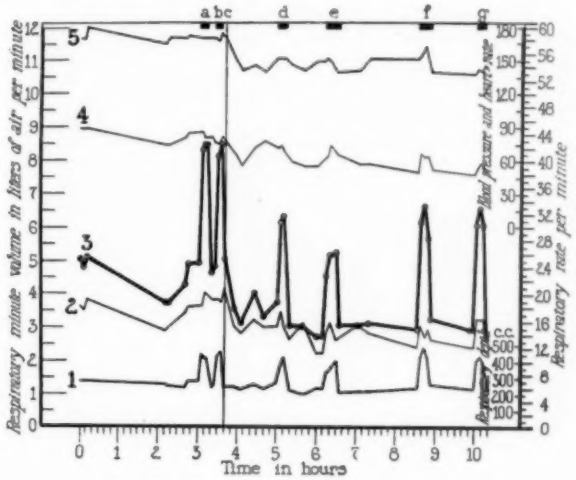
1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.

a., b., e. CO_2, 500 c.c. per minute in air.
c. Morphine sulphate ¾ grain hypodermically.
d. Sodium amytal, 260 mg., 10 per cent solution. By vein, 1 c.c. per minute.

increase in the pulse rate. The latter, however, soon returned to the normal range.

The sodium amytal was given at (f), after which the decline in minute volume was comparable to that following administration of morphine and sodium amyta- in other experiments without the scopolal mine. There was, however, a somewhat greater decrease in the depth of breathing compared to the reduction in rate. Furthermore, the response of the respiratory mechanism to the administration of carbon dioxide, was reduced more than after the morphine sodium amytal combination of other experiments. However, adequate carbon dioxide responsiveness and minute volume were retained to avoid a state of true depression. The recovery was somewhat more gradual than in the experiments in which scopolamine was not used.

Comment. The use of the scopolamine would add a desirable effect, like that of atropine, on secretions, and might further safely reduce the amount of barbituric acid necessary to produce unconsciousness and analgesia. However, the limits of


a b c d e f g
Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory rate per minute
Respiratory depth c.c.
Time in hours

Graph 10. Dog. No. 4. 14.1 kg. 10–16–29.

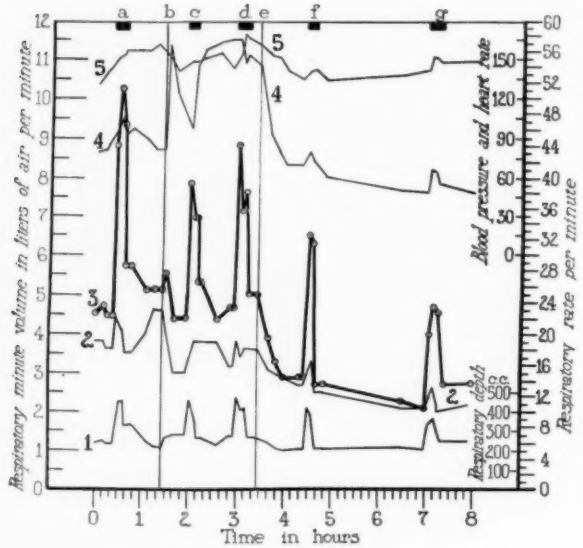
1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.

a., b., d., e., f., g. CO_2 500 c.c. per minute in air.
c. Morphine sulphate ¾ grain hypodermically.

safe dosage of scopolamine are considered to be rather narrow, especially when combined with morphine, and when followed subsequently by a general anesthetic such as ether. It does not appear to be necessary to introduce its rather variable effects among those of the morphine sodium amytal combination and sequence, especially if atropine is given to control excessive secretion.

A moderate decline in the minute volume of respiration, and in the irritability of the respiratory center to carbon dioxide, has been described. Patients sometimes appear to undergo periods of slow, shallow breathing soon after or during the administration, especially the rapid administration, of sodium amytal preceded by morphine. An analysis of the foregoing experiments indicates that the changes in respiration are largely the result of a decline in rate. Often a compensatory increase in depth occurred with only slight reduction of minute volume.

Morphine Given Four Hours before Sodium Isoamylethyl Barbituric Acid (Graph 9). The morphine was given at (c), sodium amytal at (d). The usual reduction in the minute volume of respiration after morphine and sodium amytal occurred, perhaps to a slightly lesser degree, but the reduction in the sensitivity of the respiratory center to carbon dioxide was distinctly less than in experiments in which the morphine was followed closely by the sodium amytal.


Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory depth c.c.
Respiratory rate per minute
Time in hours

GRAPH 11. Dog No. 4. 13.7 kg. 10–14–29.

1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.

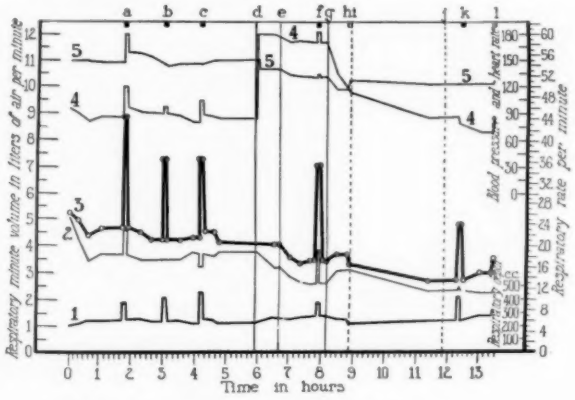
a., c., d., f., g. CO_2, 500 c.c. per minute in air.

b. Sodium amytal 260 mg., 10 per cent sol. by vein 1 c.c. per minute.

e. Morphine sulphate ¾ grain hypodermically.

Comment. The results of this and of the succeeding three experiments point to the morphine as being chiefly responsible for the changes in respiration observed after morphine and sodium amytal are given in sequence in therapeutic doses. For example, in this experiment the time allowed for the morphine to be destroyed or eliminated, was apparently important in lessening the degree of reduction of the respiratory center sensitivity, to carbon dioxide, which followed the additional administration of sodium amytal.

Morphine (Graph 10). The morphine administered at (c) resulted in a definite reduction in the minute volume of respiration, and in sensitivity of the respiratory center, in both respects equal to that seen when morphine and sodium amytal were combined. The change again was largely due to the decline in rate. The maximal effect developed about two and one-half hours after the morphine had been administered. Gradual recovery of minute volume and irritability to carbon dioxide took place.


Respiratory minute volume in liters of air per minute
Blood pressure and heart rate
Respiratory rate per minute
Time in hours

GRAPH 12. Dog No. 4. 13.7 kg. 10–29–29.

1. Respiratory depth in c.c.
2. Respiratory rate per minute.
3. Respiratory minute volume in liters of air per minute.
4. Heart rate.
5. Systolic blood pressure in mm. Hg.

a., b., c., f., k. CO_2, 500 c.c. per minute in air.

d. Sodium amytal 260 mg., 10 per cent sol. by vein 1 c.c. per minute.

e. Sodium amytal 260 mg., 10 per cent sol. by vein, 1 c.c. per minute.

g. Morphine sulphate ⅜ grain hypodermically.

h. Stimulation. To test anesthesia.

i. to j. Complete anesthesia.

l. Stimulation. To test anesthesia.

Comment. In this experiment morphine alone was followed by almost the same total changes in respiratory rate and minute volume as resulted when the morphine was supplemented by sodium amytal. The difference noted, when compared to preceding experiments, is that the decline in rate and minute volume of breathing due to the morphine, apparently, comes on

more rapidly when the morphine is followed by the sodium amytal.

Moderate Dose of Sodium Isoamylethyl Barbituric Acid and Morphine (Graph 11). Sodium amytal was given at (*b*). It was followed by a slight reduction in the irritability of the respiratory center to carbon dioxide and a rather marked increase in the pulse rate. Ample time was allowed for the full effect of the sodium amytal to become established. The morphine was given at (e). Very soon after the morphine had been given, the characteristic fall in minute volume and reactivity to carbon dioxide appeared. The change in the minute volume following the morphine, again was largely due to a decline in the rate of respiration. A notable decline in the pulse rate was observed, following administration of morphine.

Comment. In this experiment, no important change in the respiratory minute volume, other than that which could be expected at the onset of normal sleep could be attributed to the sodium amytal. Subsequently, when the morphine was administered, its characteristic effect in reducing the exchange and sensitivity of respiration appeared, apparently unintensified by the previous use of the barbituric acid compound. Therefore, special care should be exercised in the dose of morphine used, and its relation to the time and amount of the barbituric acid compound administered. In addition, particular attention should be given to the rate of respiration following the administration of these drugs in combination.

Large Dose of Sodium Isoamylethyl Barbituric Acid and Small Dose of Morphine (Graph 12). A moderate dose of sodium amytal (d) resulted in a slight decline in the rate of respiration accompanied by a compensatory increase in depth. There was no change in the minute volume. The pulse rate showed a distinct and rapid increase. Repetition of this dose of the barbituric acid derivative at (e) produced a slight but definite fall in the minute volume of respiration, due to a decline in rate, as the animal passed into a deep sleep. The sensitivity to carbon dioxide after the second dose of sodium amytal, remained practically unchanged from the normal. A small dose of morphine given at this time (g) resulted in a further decline of minute volume by additional reduction in the rate of breathing. There was also a definite reduction in carbon dioxide irritability after the morphine as indicated at (*k*). The characteristic morphine reduction in the pulse rate also appeared. It is to be emphasized that the combined effect of the small dose of morphine and the liberal amount of sodium amytal resulted in full anesthesia and relaxation which lasted for three hours, (i) to (j).

Comment. The reduction in the dose of morphine here, as compared to the dose used in the preceding experiment and the increase in dose of sodium amytal, are additional evidence to the effect that the morphine is largely responsible for the respiratory changes due to the combination.

SUMMARY

Throughout the foregoing experiments emphasis has been placed on three aspects of the function of respiration as affected by narcotizing agents.

1. The degree of impairment of the normal cooperation and coordination between the intercostal muscles and the diaphragm in the ventilatory process.
2. Variations in the minute volume as determined by accurate measurement of the rate and dept of breathing.
3. The degree to which the respiratory center is affected in its ability to respond to the stimulating effect of therapeutic doses of carbon dioxide.

With methods such as herein described and with suitable tests for determining the degree of anesthesia and analgesia, it is possible that the most advantageous proportions of morphine or other opiate, barbituric acid compounds, and local or general anesthetics, for the production of

basal narcosis and anesthesia, could be established.

Further study is to be made of the effect of larger doses of the narcotics reported; of combinations of other narcotics; and of the influence of various degrees of stimulation and depression as a result of surgical procedures.

The following summary and impressions seem justified at this time.

1. Sodium amytal was found to be very active in preventing and stopping the convulsions, and thereby the spastic paralysis of the respiratory muscles which accompanies experimental novocaine poisoning. With the convulsions eliminated, however, it did not protect against central respiratory paralysis following overwhelming doses of the novocaine. By the addition of well controlled artificial respiration, life of the animals with an efficient circulation was sustained for long periods in the instances in which central respiratory paralysis followed the large doses of novocaine, and in which animals the convulsions were prevented by the use of sodium amytal. Furthermore, preliminary medication of sodium amytal alone, or better in combination with small doses of morphine was observed to reduce the frequency and severity of untoward reactions of patients to local and regional novocaine anesthesia.

2. In the experimental work on sodium amytal as a basal narcotic for general inhalation anesthesia, quantitative determinations were made of the minute volume of respiration and of the ability of the respiratory mechanism to respond to therapeutic doses of carbon dioxide. Such determinations were considered to be of value in estimating the vital reserve, of the animals which were subjected to the effects of the various narcotizing agents.

3. Sodium amytal and other soluble barbiturates should be considered largely if not entirely as only an aid in the preparation of patients for true anesthesia which is to be induced and graduated by the use of local or inhalation anesthetics. For this purpose, complete loss of consciousness, accompanied in many cases by a variable degree of analgesia and relaxation, apparently can be safely and promptly induced by the use of a moderate amount of sodium amytal, particularly if it is preceded by a small dose of morphine or other opiate. The preliminary morphine seems to render the sodium amytal action more uniform as well as more intense, and thereby minimizes the amount of sodium amytal required. By maintaining the minimal doses of both morphine and sodium amytal postoperative unconsciousness and restlessness may be reduced. The preliminary morphine and sodium amytal together materially reduce the amount of local or inhalation anesthetic required for full surgical anesthesia, and also render induction and maintenance of the effects of the inhalation anesthetics more rapid, quiet and uniform. Postanesthetic nausea and vomiting are extremely uncommon.

4. The use of sodium amytal or other soluble barbiturate in suitable combination and sequence with morphine, or alone for the production of basal narcosis may be accompanied by a higher degree of vital reserve than prevails when local or general anesthesia is induced without preliminary medication. This is indicated by the fact that experimentally, in the presence of such basal narcosis, full surgical ether anesthesia was accompanied by a comparatively slight reduction in the minute volume of respiration, a slow but deep and efficient type of breathing, and only a slight reduction in the carbon dioxide irritability of the respiratory center. The fact that minimal amounts of a number of similarly acting drugs were used in combination, with probably slightly different sites of most intense action, rather than relatively large and depressant amounts of any one narcotizing agent, may be of importance in this connection. The elimination of apprehension and induction excitement in patients might also play a part in lessening an often unrecognized or unexpected tendency to shock reaction. On the other hand, it should be remembered

that the combined effects of similarly acting drugs may assume alarming proportions, especially if the dose of each drug is not carefully curtailed and regulated to its desired effect.

5. Basal narcosis as a result of the proper administration of sodium amytal in combination and sequence with morphine, and unaccompanied by morphine in many instances, is followed by amnesia on the part of the patient for the anesthetic and surgical procedures, and for a large part of the preoperative and postoperative discomfort. This action alone is worthy of intensive study and application.

Finally, it may be said that in view of both experimental and clinical evidence, intravenous anesthesia in its broad sense, unsupplemented, uniform, safe and satisfactory to the best interests of the patient, surgeon and anesthetist, is not yet an established fact. Nevertheless, by the use of a judicious combination and sequence of hypnotics, narcotics, local and inhalation anesthetics, it is possible to accomplish every desirable purpose that could be fulfilled by any intravenous anesthetic.

I desire to express my appreciation to Dr. Rowntree, Dr. Lundy, and the Mayo Clinic for their invaluable assistance in the conduct of this investigation, and for the privilege of doing the work in their laboratories.

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CLINICAL EXPERIENCES WITH THE INTRAVENOUS INJECTION OF SODIUM ISOAMYLETHYL BARBITURATE AS AN AUXILIARY ANESTHETIC*

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AMERICAN medicine is credited with having contributed one of the most important advances in surgery introduced in the last century. Since that memorable day of October 26, 1846, when a group of surgeons at the Massachusetts General Hospital stood anxiously by while a dentist deliberately administered inhalations of ether to prepare a patient for a major surgical procedure,[1] many developments in anesthesia have occurred. Some twenty years later, this epochal contribution to surgery by a dentist was reciprocated in part by that master surgeon, William Stewart Halsted,[2] who was the first to make possible the extraction of teeth, and later other operations, by the injection of cocaine as a local anesthetic. In 1885, Corning's[3] discovery of spinal anesthesia opened up another avenue of development, and recent advances in this field[4] are proving to be of inestimable advantage in operative surgery.

Despite these improvements, surgeons, chemists and pharmacologists are still seeking the ideal anesthetic. What, we may well ask, is the ideal anesthetic? In relieving the patient of pain and mental anguish during the operation, the ideal anesthetic will not bring added terrors of its own. The patient will not remember the anesthetizing process as a hideous nightmare, and the worst part of his operative experience. The postoperative nausea of ether still remains one of the most revolting memories that the patient retains, the mere thought of which literally turns his stomach inside out.

Secondly, the ideal anesthetic will induce anesthesia as gently, as quietly and as naturally as sleep itself. No longer will the patient be plunged into a seemingly endless eternity after a short period of consciousness, and therefore terrifying, struggle against suffocation. Anyone who has been put to sleep consciously will recall the experience only with repugnance.

Thirdly, it will be an anesthetic without irritation to organs of the body in its administration and elimination. It will not add to the hazards of the operation by inimical effects of its own such as ether produces in the air passages, chloroform upon the liver, and cocaine upon the nervous system. After the administration of the ideal anesthetic it will be impossible for a surgeon to shrug his shoulders, sidestep all responsibility and mutter accusingly, "ether pneumonia."

Bearing these requirements in mind let us consider what have been our experiences with the most recent addition to our anesthetic armamentarium, namely sodium isoamylethyl barbiturate.[5,6]

Our clinical experience so far covers a group of 150 general surgical cases in which sodium amytal has been employed as an auxiliary anesthetic. There are such very real objections to its use in sufficient quantity to produce of itself complete surgical anesthesia, that we have avoided using it as the sole anesthetic. Briefly, these objections center about its depressing effects upon the circulatory and respiratory centers, and more particularly upon the prolonged continuance of the anesthetic state beyond the operation. When it is administered in full anesthetic doses, the patient may continue in the unconscious state for twelve to eighteen hours. Constant nursing supervision is required to prevent asphyxiation from a relaxed jaw

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and tongue. The intake of fluids is prevented, voiding is omitted, and it is difficult to keep the respiratory passages clear of the accumulating mucus. Moreover, in larger doses, the shallow breathing and drop in blood pressure strike such terror to the surgeon as well as to the anesthetist that we cannot recommend its use as the sole anesthetic. Our experiences, therefore, deal only with cases in which the sodium amytal has been supplemented by a local anesthetic or by nitrous oxide and oxygen, and to a very minor degree by ether.

When employed in conjunction with infiltration of the operative area with novocaine, certain serious objections have arisen. Clinically it is well known that the barbiturates are particularly useful in counteracting the toxic and convulsive effects of cocaine. Disastrous and fatal poisoning from cocaine may be forestalled by the preliminary administration of barbital either by mouth or subcutaneously, as advocated by Martin.[7]

A similar antagonism is noted when a barbiturate is employed in conjunction with novocaine. The patient, who has fallen into a deep sleep with the administration of the amytal, suddenly appears to waken after the first few cubic centimeters of novocaine have been injected. Painful stimuli cause uncontrollable struggling and the only way out has been the addition of nitrous oxide anesthesia.

The successful use of a local anesthetic is dependent to a certain degree upon the cooperation of the conscious patient. The ungoverned and irresponsible actions of a patient who is only half asleep and half conscious are obviously to be avoided. It is preferable, therefore, when contemplating its use with novocaine to give only sufficient amytal, 4 to 6 grains, to produce drowsiness, from which the patient may be easily aroused to assist and cooperate with the surgeon. When applied in this way it has been found of very definite advantage in operations upon the nasopharynx in individuals who are of a very nervous, excitable temperament, whose gag reflex is extremely sensitive and to whom the surgeon does not wish to give a general anesthetic. The operation is less of a fight and more of an artistic accomplishment when such patients are made drowsy by the use of sodium amytal, or if you like, by scopolamine and morphia. It would appear that the range of operation to be performed on the nasopharynx under local anesthesia can be materially extended to a larger group of patients by the addition of small doses of sodium amytal.

In our experience thus far its greatest usefulness has been in extending and facilitating the use of nitrous oxide anesthesia. The usual preliminary preparation with morphine and atropine is employed. On arrival in the operating room, the sodium amytal is introduced intravenously at the rate of 1½ grains per minute, or even more slowly. The amount so administered varies remarkably with different patients, there being a very definite individual susceptibility to the effect of the drug. This is apparently true of all the barbiturates. Accordingly, the drug is slowly administered until the patient is fully asleep, the amount varying usually from 7 to 12 grains. An additional 3 to 5 grains are then administered beyond the amount necessary to induce sleep. In one man weighing 180 lb. with a severe secondary anemia and 40 per cent hemoglobin, sleep was induced after only 5 grains had been administered, whereas another patient, a spare woman of 115 lb., received 20 grains before she showed any evidence of going to sleep. Obviously to administer the drug according to body weight would be quite absurd. The usual dose for the adult as employed at present at the Stanford Clinic is from 7 to 12 grains although Lundy at the Mayo Clinic has given as high as 45 grains with impunity.

A second guide as to the amount of the drug to be administered is its effect upon the general blood pressure. The usual fall is from 20 to 40 points, the maximum fall occurring at the moment the patient goes to sleep. When the fall in blood pressure is

abrupt and great, its administration is immediately discontinued. It is our belief that a personal idiosyncracy to the drug is manifested by a profound effect upon the blood pressure, and any fatality from this cause should be avoided by carefully checking the blood pressure during the administration of the drug. Sleep is induced without the slightest struggling, the patient dropping off as naturally as in normal sleep. The patient is wheeled into the operating room, where the field is prepared and draped. At any moment, if the patient becomes aroused, the nitrous oxide is begun, usually in full concentration at first, but after the incision through the skin has been completed a leaner mixture is required with often as high as 30 per cent oxygen. It is believed that the actual total amount of nitrous oxide necessary for continued anesthesia is correspondingly decreased. Abdominal operations may occasionally be performed without the addition of ether, although in several instances a small amount of ether was found necessary to secure the necessary relaxation of the abdominal wall for the approximation of the peritoneum and posterior sheath of the rectus.

Upon the withdrawal of the nitrous oxide at the completion of the operation the patient may usually be easily aroused, but he drops promptly to sleep when transferred to a warm bed. After these smaller doses of the drug, the patient can always be aroused to void, to take fluids and to clear his throat. There is, however, an amnesic period of from twelve to eighteen hours of which the patient remembers little, and he often wakes up from his experience, wondering when the operation is to be performed. During this period, a nurse is in constant attendance and the patient is kept on one side to prevent swallowing of the tongue and asphyxia.

If at the end of the operation the blood pressure is low, ephedrine sulphate is administered in doses of $\frac{3}{8}$ and $\frac{3}{4}$ grain. A restless, half-unconscious patient may often be fully aroused by giving ephedrine and rather large doses of 8 to 10 grains of caffeine sodium benzoate. This combination of ephedrine and caffeine is considered the best and really only antidote available. If there is marked restlessness after the operation with delirium, morphia may be administered to excellent advantage.

In the highly nervous patient, as in exophthalmic goiter, the drug is administered in the patient's room and the patient avoids the terrifying experience of approaching the operating room.

As a rule, the patients exhibit very little nausea and vomiting after the operation, even after the intra-abdominal procedures. The nurses have claimed that the amount of care following the use of amytal is definitely decreased during the first twelve to eighteen hours following operation.

In addition to its use as an adjunct to general anesthesia, sodium amytal is of distinct value in other clinical fields. Drabkin[8] and Robbins[9] et al have recently reported their experiences in the field of obstetrics.

Numerous other clinical applications of the barbital compounds including amytal have been recorded by Weiss[10] and Lundy.[6] In certain types of psychoses sleep has been maintained for as long as forty days on a dosage of 5 to 10 grains daily. Postoperative psychoses have been successfully controlled. Status epilepticus has been controlled by 6 to 15 grains of sodium luminal administered intravenously.

The toxic manifestations of cocaine such as convulsions may be immediately dispelled by the intravenous injection of 7 to 15 grains of sodium luminal or amytal. In tetanus, the generalized spasm of the musculature with recurrent convulsions may be controlled and the patient spared a terrifying experience by the intravenous injection of 10 to 20 grains of sodium amytal.

Persistent hiccups have been controlled by amytal. Intense pain unrelieved by morphia has on occasion yielded to the intravenous injection of 10 to 15 grains of

amytal as in a case of a broken back, a case of extensive burns which ended fatally, and a case of gastric crisis. A patient with severe generalized pruritus from jaundice was kept comfortable by the administration of 4 grains by mouth at four-hour intervals. Postoperative convulsions following a craniotomy yielded to small doses by vein, as also convulsions following cranial injuries. MacCallum[11] found it of value in the treatment of delirium tremens, and Mehrtens[12] in the treatment of drug addiction.

Summarizing these clinical experiences with amytal we may say that it provides a convenient way of administering the purified drug in many situations in which prompt sleep or prompt relief from pain or convulsions is desired.

As an anesthetic, however, it is subject to definite limitations. Once injected into a vein, it cannot be retrieved, and to date it is difficult to counteract the drug once it has been administered. Ephedrine (grain ⅜ to grain ¾) and caffeine sodium benzoate (grains 7 to grains 10) are the only agents available to counteract the effects of the drug.

The occasional restlessness and mild delirium after operation are a definite disadvantage but are usually absent when amytal is administered in the smaller doses of from 7 to 12 grains. When present restlessness should be controlled by morphia.

The drop in blood pressure is a distinct disadvantage. Even with small doses this drop may be alarming and sufficient to warrant postponement of the operation. It may be an evidence of an individual idiosyncrasy to the drug, and its possible appearance makes imperative frequent observations on blood pressure during the administration of the amytal. It is our opinion that once a fall in blood pressure has occurred, the stability of the vasomotor center has been slightly impaired and a second drop is more likely to occur. The disadvantage of this is obvious when shock and an accompanying fall in blood pressure are likely to result from the operative procedure itself.

The use of sodium amytal is avoided or limited to small doses in operations upon the jaw, tongue or mouth, since any postoperative drowsiness would prevent the proper expectoration of saliva or mucus which invariably accumulates in the throat following such procedures.

Its advantages in the operating room may be briefly summarized as follows:

1. Amytal provides the normal induction of a natural sleep without the apprehensive struggling of a conscious patient. A patient may be put to sleep in his own room and return to the room without any knowledge of ever having left it.

2. All preparation of the patient with respect to position on the table, cleansing and draping of the operative area may be performed before the administration of the inhalation anesthetic.

3. There is a marked reduction in the amount of nitrous oxide that is necessary to produce full anesthesia, and cyanosis is avoided. The amount of oxygen which can be added to the nitrous oxide-oxygen mixture is increased, the percentage varying between 16 to 32 per cent oxygen.

4. With the use of amytal we may avoid the struggling on the part of certain apprehensive patients who cannot be kept fully anesthetized on nitrous oxide alone without marked cyanosis or without the addition of ether.

5. Abdominal operations may be performed without local anesthesia under nitrous oxide inhalation, with the addition of a slight amount of ether while closing the peritoneum.

6. There is a marked reduction in postoperative nausea, in the postoperative struggling of a patient and in postoperative care.

7. Patients remain amnesic for twelve to twenty-four hours and become fully conscious at the end of this period with very little remembrance of the operation or the immediate postoperative period. The need for postoperative morphia is greatly reduced.

8. Patients who had experienced other operations under ether anesthesia claimed that sodium amytal rendered their present operation a pleasant experience in marked contrast to the ordeal through which they had previously passed.

In operations upon patients with exophthalmic goiter, and upon the very apprehensive and easily excitable patient, sodmiu amytal has, we believe, a very definite place in anesthesia, and may be used in doses of 7 to 12 grains with definite advantage to the patient. From our brief experience, however, it is obvious that the ideal anesthetic, as originally described, is not yet available.

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INDUCTION ANESTHESIA BY SODIUM AMYTAL*

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THE number and variety of anesthetic agents being employed today are an evidence of the fact that the ideal method has not yet been developed. Surgeons generally are giving greater thought and attention to the proper selection of the anesthetic. In conjunction with the anesthetist, the choice of procedure is made on the basis of the individual requirements of a given case. The proper determination of the type of anesthesia is of equal importance to the performance of the technical procedure of the operation.

Inhalation anesthesia, administered under the most approved methods, has certain distinct disadvantages. Chief of postoperative sequelae are the occurrence of respiratory complications, nausea and vomiting. Patients suffering from diabetes, nephritis, alcoholism, pulmonary infections and shock, are not good subjects for general anesthesia.

The employment of spinal anesthesia has become quite extensive during the past few years and its popularity is increasing steadily. The appreciation of its wide range of applications, its safety and the better knowledge of its technical application and possible dangers, are more general in acceptance. The pioneer work of Labat, Babcock and Pitkin has done much to enlighten the profession in the proper employment of spinal anesthesia.

In the past eighteen months, a series of over 200 patients of all kinds have been operated on, with the employment of spinal anesthesia alone. Our satisfaction with its employment increases with experience. In abdominal work, the relaxation obtained facilitates technical manipulation and speed in accomplishment, lessening the need for employment of pads, thereby preventing some of the postoperative adhesions. The lessened occurrence of postoperative respiratory complications is striking, only 1 case of pneumonia having developed in our series.

In unskilled hands, it has definite dangers and should be used with care and discrimination. Observance of technical details, skill in the administration, proper teamwork by operator, anesthetist and nurses, are essential.

With some patients various conditions, such as undue apprehension, unstable psychic poise, thyroid toxemias and a variety of contraindications to the patient's knowledge of the personnel and environment of the operating room exist. In such a group, the induction anesthesia by means of the intravenous injection of an aqueous solution of sodium amytal is of great value, in conjunction with a supplementary spinal or gas oxygen anesthesia. The advantage of the intravenous over oral or rectal administration is the speed and ease with which sleep is induced. It also results in more accurate dosage as individual susceptibility varies, the administration being terminated when the desired depth of sleep and relaxation is obtained.

The analgesic effects of the barbituric group of drugs, to which belong veronal, luminal and sodium amytal, are well known, as is the antidotal action of this group for procaine, which may account for the fact that fewer toxic manifestations were noted in the amytal intraspinal than in the intraspinal anesthesias alone.

The experimental work of Zerfas and McCallum of Indianapolis, first called attention to its practical possibilities. DeTakas of Chicago and Brown of Santa Barbara, have reported their experience with its use. We have observed its practical demonstration by Sise of the Lahey Clinic of Boston and Buchanan at the New York Post-Graduate Hospital. Our

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own experience comprises a group of 40 cases in which sodium amytal was used, at the Memorial Hospital, Orange, New Jersey.

Sodium amytal alone may be sufficient for the anesthesia required for minor surgical procedures, such as, dilation and curettage, hemorrhoidectomies, intrauterine application of radium and for making differential diagnoses of abdominal and pelvic conditions in patients difficult to examine. In one patient, a woman of twenty, presenting symptoms of an acute lower abdominal lesion, the differentiation between an acute appendicitis and salpingitis was made certain by the aid of the complete relaxation obtained with the use of 0.6 gm. of sodium amytal. The ovary and an enlarged tube were palpated, a gangrenous unruptured appendix lying low in the pelvis, was recognized and prompt surgical attention was followed by a good result. In the small dosage employed in our cases, (the average dose being 0.8 gm. and the maximum being 1.0 gm.) it was found insufficient for major work and was supplemented by spinal or gas oxygen anesthesia.

Many patients fear an anesthetic more than an operation. To some, the journey from the bedroom to the anesthetic room in the operating department, offers an unwelcome experience. The ease and comfort of the production of a quiet profound sleep, by simple intravenous injection, are most acceptable to the patient. The approval of such a means, by harassed and anxious relatives, is positive.

Experience has demonstrated that the employment of a hypnotic the night before, insuring a preliminary rest and affording an opportunity to detect any unusual susceptibility to the barbital compounds, is advisable, veronal and luminal being employed. A preliminary hypodemric of $\frac{1}{6}$ grain morphine and $\frac{1}{150}$ grain atropine makes the patient still further receptive. The effect of sodium amytal on the respiration is to make it slower and more shallow. If undue depression is manifest, the inhalation of CO_2 and oxygen will quickly restore it to normal. The pulse rate is made slower, the effect on the blood pressure is usually pronounced and the average in our series was a reduction of 46 mm. systolic and 23 mm. diastolic. The greatest fall was a reduction of 150 mm. in systolic and 70 mm. diastolic in a case of tetanus in which it was employed. This case well demonstrated the antispasmodic effect of the drug. Violent tetanic convulsions were completely controlled by the use of 2 gm. One grain of ephedrine given hypodermically restores the pressure to normal promptly. In all cases this was given with the local infiltration of novocaine, prior to administration of the spinal anesthesia.

Following is a brief synopsis of observations noted in 40 cases.

Ward cases	18
Private cases	22
Oldest patient	70
Youngest patient	14
Average age	40
Shortest period narcosis	1½ hr.
Longest period narcosis	22 hr.
Average period narcosis	7 hr.
Cases with amytal alone	5
Cases with spinal anesthesia	28
Cases with spinocaine	18
Cases with neocaine	10
Cases with gas, oxygen	7
Average dose spinocaine	3½ c.c.
Average dose neocaine	.14 gm.
Nausea and vomiting following	9
Cases requiring catheterization	4
Cases of mild delirium	4
Hysterectomies	6
Appendectomies	4
Salpingectomies and appendectomies	2
Salpingectomy and oophorectomy	1
Exploratory laparotomies	3
Implantation of radium	1
Dilatations and curettages	2
Double salpingectomy	1
Herniotomies	2
Cholecystectomies	9
Amputation (leg)	1
Hemorrhoidectomy	1
Uterine suspensions	3
Vaginal examinations	2
Perineorrhaphy	1
Tetanus case	1

SODIUM AMYTAL IN GENERAL SURGERY*

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SODIUM amytal is a valuable drug for many purposes. Its action and uses may be best understood by considering it a splendid intravenous hypnotic instead of an anesthetic.

After an experience of 22 cases we prefer to use it as an adjuvant only to nitrous oxide, ether or novocaine locally. We have not yet used it with spinal anesthesia but believe it would be perfectly safe and very valuable for high-strung and nervous patients who are restless under spinal anesthesia alone.

Our preliminary preparation has consisted of 10 grains of chloretone at nine P.M. of the day preceding operation and 10 grains of chloretone at seven A.M. on the day of operation. A hypodermic of morphine 1/6 grain or 1/4 grain is given a half-hour preceding operation. There seems to be some respiratory depression from sodium amytal so the patient should not be over morphinized. We have not seen any ill effects from these doses. The dose varies with the weight of the patient.

Theoretically it would be almost ideal to give sodium amytal to the patient in his own bed before he is placed upon the stretcher and carried to the operating room. This would eliminate much of the fear and nervousness of sensitive patients. We have found it to work well and when it is given this way, the patient has no knowledge that the operation has been performed. We thought that it could be given in a general ward behind screens without the other patients realizing that anything unusual was taking place but found that it created much interest in the other occupants of the ward. The reaction was interesting, however, for the patient in the next bed, who was to be operated upon later, remarked "I wish that you would do it to me like that." As a routine procedure it adds somewhat to the work and there is the disadvantage that the narcotized patient should not be left alone with a nurse, who is not especially trained for the purpose, during the trip from the bed to the operating room.

We have usually administered the sodium amytal in the operating room. The standard dose is 1 gm. dissolved in 10 c.c. of distilled water. After a clear and colorless solution has been obtained it is given intravenously. The anesthetist takes the blood pressure and calls off the half minutes during the injection which should take ten minutes. A comfortable position, with both elbows supported and the tip of the index finger of the left hand resting upon the hub of the needle, allows relaxation. A careful watch is maintained for the moment when unconsciousness first supervenes. This is the index of the patient's susceptibility to the drug. If 4 c.c. of the solution have been given the response is normal, for most individuals are sound asleep at this time. If a little of the mixture enters the subcutaneous tissue it need occasion no alarm for we have had no sloughs from such an accident. When snoring commences the head is turned to the side and extended to prevent the base of the tongue from dropping back.

There is an occasional case that requires nothing in addition to the sodium amytal for an appendectomy or herniorrhaphy but nearly every patient who receives only 1 gm. of the drug will require a little ether, nitrous oxide or ethylene in addition. The anesthetists say that the amount required is about 1/3 that usually given alone. One hysterectomy needed only 6 drs. of ether after the sodium amytal. A cholecystectomy had 5½ oz. of ether by the wasteful open drop method for an operation that took nearly an hour. When

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SERIES OF SODIUM AMYTAL CASES

Hosp. Number	Operation	Dose of Amytal (Grams)	Supplemental Anesthesia	Complications
36081 Norwegian H.	Appendectomy	1	0	Granular casts and albumen. Normal three days later
135449 Methodist H.	Appendectomy	1	Nitrous oxide	Toxic dermatitis
136472	Appendectomy	1	Nitrous oxide	0
136539	Appendectomy	1	Nitrous oxide	0
136548	Appendectomy	1	Nitrous oxide	0
136603	Appendectomy	1½	0	0
136651	Appendectomy	1	0	0
134672	Cholecystostomy	1½	Nitrous oxide	Edema of lungs. Dilated heart. Died
135527	Cholecystectomy	1	Nitrous oxide	0
136594	Cholecystectomy	1	Ether 5 oz.	Infection tube drainage tract.
136721	Cholecystectomy	1	Ether 2 oz. Nitrous oxide	Infected gall bladder. Wound drained. Pus later
136745	Cholecystectomy	1	Ether ½ oz.	Severe bronchitis
37379 Norwegian H.	Hysterectomy	1	Ether 7 drs. Nitrous oxide	0
135107	Myomectomy Appendectomy Release intestinal adhesions	1	Nitrous oxide	Infected wound
135391	Pelvic repair Appendectomy Coffey suspension	1	Nitrous oxide	0
135530	Dilatation Curettage Insertion radium	1	0	Flighty. Muscular twitching. Hysterical 24 hours after op. Cured by morphine sulphate
134629	Herniorrhaphy	1	Nitrous oxide	0
134766	Herniorrhaphy, bilateral	1½	0	0
136592	Herniorrhaphy, bilateral	1½	0	0
135471	Gastroenterostomy	1	Ether 2½ oz. and nitrous oxide	Postop. pneumonia. Recovered
136635	Wiring fractured jaw (contraindicated)	1	0	Cyanosis and poor breathing. Relieved by traction on tongue
136597	Subtotal thyroidectomy	1	Nitrous oxide	Infected wound

used with sodium amytal a little gas will give a relaxation that is not seen without it. These small amounts of the additional anesthetic must mean less concentration in the blood, less saturation and poisoning of the tissues and a more rapid and less damaging elimination. Our experience verifies this. Vomiting is very rare during the first twenty-four hours and in most cases never occurs at all during convalescence.

An occasional case shows rather marked restlessness bordering on delirium as the patient awakes from sleep. This is unpleasant, if allowed to continue, but it yields very promptly to a hypodermic injection of morphine and does not recur.

It probably happens in less than 10 per cent of the cases. The time of awakening averages about six hours after the 1 gm. doses. It varies from two to ten hours. Some patients wake up, ask for a drink, turn over and then sleep for five or six hours longer. There is seldom any complaint of pain within the first twelve hours.

The operative wounds heal kindly. The blood chemistry does not show any marked changes. The urine usually is concentrated for a day or two and shows a faint trace of albumin. The tongue may be a little coated and dry, possibly from breathing through the mouth. In forty-eight hours there is a close approach to normal.

Complications. These cases were all operated upon during the winter months when the incidence of respiratory infections is always high. The shallow respirations and mouth breathing induced by sodium amytal may possibly favor such complications although the average time before awakening was only six hours.

There has been only one death in our series. This was a man thirty-eight years old, an alcoholic, as we discovered later, who was operated upon with the mistaken provisional diagnosis of acute cholecystitis. He showed a positive direct and indirect Van DenBergh test. His icteric index was plus seventy. He received 1½ gms. of sodium amytal but it was necessary to use additional nitrous oxide because he moved during the operation. An advanced cirrhosis of the liver was found without cholecystitis. He died twelve hours after operation from edema of the lungs and a dilated heart. He was fully conscious for several hours before death and was never deeply unconscious so that he could not be easily aroused. Doctor Eli Lilly, under date of January 14, 1930, says, "So far as we know there have been no deaths directly attributable to Amytal . . . Such would seem to be the situation in your case."

The toxic dermatitis, seen in one case, we believe was caused by the sodium amytal. So also was the transient renal irritation found in the first appendicitis case.

This drug should not be given in cases of fractured jaw when the jaws are to be wired and the tongue may drop back.

The thyroidectomy for hyperthyroidism followed the regular rule that these patients will tolerate relatively large doses of the sodium amytal. After 1 gm. had been given the patient still moved her head and she was conscious and moved as soon as the operation had been completed and the nitrous oxide discontinued. Her unusually rapid convalescence causes one to wonder if sodium amytal may be chemically and physiologically antagonistic to thyroxin and by neutralizing it prevent postoperative hyperthyroidism. However, "One swallow doesn't make a summer."

Several clean cases showed some wound infection following operation but sodium amytal did not cause this. There was a mild hospital flurry of infections on several different services at the time. Most of the cases did not receive sodium amytal.

Conclusions. Sodium amytal seems to be a safe and valuable ally in general surgery when used in moderate doses. It allays nervousness and apprehension; reduces the amount of ether or nitrous oxide to a negligible quantity; gives an easy, painless recovery without vomiting during the first hours following operation and leaves the memory free from the disagreeable impressions so often left after many operative procedures.

INTRAVENOUS SODIUM ISOAMYLETHYL BARBITURATE WITH SPINAL ANESTHESIA*

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SPINAL anesthesia has proved itself to be so valuable that it has become an essential part of the activities of every well organized anesthesia department. The reaction of different individuals to the conscious state during an operation under this anesthesia varies considerably. Some do not object to it and are even interested to know what is going on. Most people, however, prefer unconsciousness or at least some dulling of consciousness. The position on the table for an abdominal operation is uncomfortable, especially if the operation is at all prolonged. Various sounds, such as the click of forceps, the gurgling of intestines, the noise of the suction apparatus, and the talk of the surgeon are unpleasant, and to the apprehensive may be extremely disturbing. With most patients, therefore, a certain amount of narcosis is highly desirable.

There are a few patients who are so apprehensive and whose nervous systems are so constituted that the conscious state during an operation under spinal anesthesia, particularly an abdominal operation, even with some narcotic medication, constitutes a mental ordeal to which they should not be subjected. This was particularly borne in upon me in interviewing a lady before her operation under spinal anesthesia. She recounted to me how a friend had told her that she had heard a surgeon ask for a knife during her operation. My patient said that this incident seemed to her so horrible that she could not credit it as being possible. I believe that we who are inured to operating room procedure cannot appreciate what an abdominal operation in the conscious state means to such an individual, but I do feel quite sure that such individuals should not be conscious during their operation.

It is customary before most operations to give a certain amount of quieting medication. In our early work with spinal anesthesia we found that a large number of patients, in spite of this preliminary medication, objected to the mental aspect of being operated upon under spinal anesthesia. We, therefore, gradually increased the amount of preliminary medication and found that this materially helped the mental condition of the patient. This procedure has worked out very well with the majority of patients; but there is a small group with whom it has not been so successful. This group constitutes the apprehensive and hypersensitive individuals to whom I have already referred.

This group was not satisfied unless they were rendered entirely unconscious. But, in the attempt to get a sufficient amount of preliminary narcotic medication in the usual way to produce this effect, certain difficulties were encountered. It was found that the effect of a predetermined dose of narcotic drugs varied so much with different individuals that it was impossible to gauge its effect with sufficient accuracy. In spite of our best efforts, some of the patients remained conscious, while others fell into such deep narcosis that an undesirable degree of depression resulted. Many, whether unconscious or not, had skin sensation so dulled that it was impossible to determine before operation the extent of the spinal anesthesia. This, we felt, it was quite important to determine, because if the spinal anesthesia was not already high enough, we could raise it by shifting the position of the patient. We found that the great majority of our failures to get proper height of anesthesia with spinal occurred in these cases and was due to a deceptive skin test. We thought that we

* From the Lahey Clinic, Boston, Massachusetts. Submitted for publication, June 24, 1930.

had gotten the anesthesia high enough, but found when the operation started that we had not.

These difficulties have been entirely overcome by the use before operation of intravenous sodium isoamylethyl barbiturate. In the first place, the effect of the drug can be gauged quite accurately so that patients are seldom either too light or too deep. The intravenous route causes the drug to enter the circulation very rapidly so that a maximum effect is produced immediately. On the conclusion of the injection this effect lessens quite rapidly for a short time and thereafter so slowly that for purposes of the operation, it remains practically constant. This lesser degree of narcosis is the one which we want to obtain. While allowance must be made for this lessening of narcosis immediately following the injection, yet the degree of lessening appears to be so constant that with a little practice the proper allowance can readily be made. To get the desired degree of narcosis, we adopt roughly the following procedure: Injecting the drug slowly, we wait until the patient is unconscious, with absent lid reflex, and usually with a little stertor, and then inject about 25 per cent more than we have already given, when the skin reflex will usually be found to be abolished. The amount of the drug necessary to accomplish this is usually about 0.6 to 1.0 gm. A few patients will become restless during operation, even though still unconscious. This restlessness can usually be controlled, if taken early, by 1/6 to 1/4 grain of morphine, sometimes with the addition of nitrous oxid for a few minutes.

The second advantage of this drug is that we can readily test for the height of anesthesia. I can recall but 2 cases in which this was not possible. Due to the rapid lessening of narcosis already mentioned it is found that by the time spinal anesthesia has been given, skin reflexes have returned, so that test for anesthesia can readily be made. Indeed, by this time, in spite of the fact that the patient is entirely unconscious, skin reflexes are quite lively so that no doubt whatever exists as to the height of anesthesia. This we feel is quite important.

This narcosis has, of course, the advantages and disadvantages common to the use of sodium isoamylethyl barbiturate. As the dose of the drug is not large, however, the disadvantages are not prominent and they are much more than counterbalanced by the advantages of unconsciousness and skin sensitivity, together with other advantages such as lack of vomiting both during and after operation, and the presence of considerable postoperative amnesia.

The technic of intravenous injection is that usually employed with this drug and need not be detailed here. A few points, however, do require special mention.

With this drug given intravenously, a certain amount of fall in blood pressure is to be expected. A fall in blood pressure just preceding the administration of spinal anesthesia is undesirable. With the young and vigorous this fall is slight and the pressure soon returns to normal. This condition need cause no concern. With the weak and elderly and especially with the hypertensive and sclerotic this fall, however, may be considerable and the pressure may return grudgingly if at all towards normal. Such patients make poor subjects for this procedure.

Between these two extremes lie the great majority of patients. These patients get a slight to a considerable fall of pressure, yet with a little care will make good subjects for spinal anesthesia. If one but waits a while, the pressure will return toward normal. This, however, is a waste of time and is unnecessary, as the pressure can be kept from falling by the use of ephedrine. Ephedrine is commonly given as a prophylactic before spinal anesthesia and can just as well be given a little earlier, with the sodium isoamylethyl barbiturate. If the contents of the usual ampule of ephedrine, containing 50 mg., are added to the usual amount of sodium isoamylethyl barbiturate, namely: 10 c.c. of a 10 per

cent solution, the drug will be precipitated and a slight murkiness will result. This is undesirable. Approximately half this amount, however, 25 to 30 mg., can usually be added without causing precipitation. If this amount of ephedrine is given intravenously with the narcotic drug, the resulting drop in pressure will usually be absent or negligible. A few susceptible individuals will get a moderate fall in pressure in spite of this. If it is suspected that the individual belongs to this class, it is well to give the other half of the ampule of ephedrine, namely 25 mg., subcutaneously before starting the intravenous injection.

With some experience, care and discrimination, it will be found that patients can be quite consistently brought to the operating table for spinal anesthesia entirely unconscious, retaining active skin reflexes, and with little or no fall in blood pressure.

This procedure is especially applicable to the extremely nervous and apprehensive who are young and in good condition. It is not suitable for the very elderly, hypertensive or sclerotic.

CONCLUSIONS

This procedure has the disadvantages common to the use of sodium isoamylethyl barbiturate and to that of spinal anesthesia. Its field is somewhat narrow and limited; but in its field, with hypersensitive individuals, in good condition and having an abdominal operation, it has many advantages. It gives them the greatest possible comfort over the trying period of operation, the best possible operating conditions for abdominal surgery, and withal the comparative absence of toxic or injurious effects on the tissues and functions of the body.

SUPERFICIAL CERVICAL PLEXUS BLOCK ANESTHESIA FOR THYROIDECTOMY*

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MADISON, WISCONSIN

GAS-OXYGEN anesthesia for thyroidectomy has the disadvantage of causing vascular engorgement and, therefore, a more soiled operative field than local anesthesia. Infiltration anesthesia is superior to gas in many respects, but it has been supplanted at the Jackson Clinic by the superficial cervical plexus block because of the many advantages of the latter method. Many technics have been described for both superficial and deep cervical plexus blocks. Although they produce a satisfactory anesthesia, they are difficult to execute and require multiple needle punctures into parts of the neck richly supplied by large blood vessels.[1,2,4]

FIG. 1. Initial intradermal wheal of 1 per cent novocaine raised just lateral to sternal origin of sternocleidomastoid muscle.

TECHNIC

A hypodermic of pantopon grain ⅓ and scopolamine grain 1/200 is given one hour before operation. Ten grains of sodium barbital is also given by mouth to reduce the toxicity of novocaine, in case of accidental intravenous injection.[3] Pantopon grain ⅓ may be repeated immediately before the anesthesia is induced. The surgical field is prepared and a 27 gauge 1 in. needle is used to raise an initial wheal of 1 per cent novocaine just lateral to the sternal origin of the sternocleidomastoid muscle on each side. The patient's head is then turned to one side and the neck extended, stretching the sternocleidomastoid muscle, and a 4½ in. 22 gauge needle is inserted through the skin wheal. The needle is then gently passed up just posterior to the belly of the sternocleidomastoid muscle almost as far as the mastoid process. Palpation of the tip of the needle through the overlying skin helps to keep it superficial during insertion. About 15 c.c. of 1 per cent novocaine is injected during the withdrawal of the needle. The needle should be kept in motion during injection to avoid intravenous injection of novocaine with its attendant dangers.

FIG. 2. Patient's head is turned to one side and extended, stretching sternocleidomastoid muscle. A 4½ in., 22 gauge needle is inserted through skin wheal and gently passed up just posterior to sheath of sternocleidomastoid muscle. Palpation of tip of needle through overlying skin helps to keep it superficial.

FIG. 3. About 15 c.c. of 1 per cent novocaine is injected while slowly withdrawing needle.

Anesthesia of the anterior three-fourths of the neck from the sternal notch to the tip of the chin is complete within five minutes. It is sufficient to permit thyroidectomy without pain, if the superior poles of the gland are infiltrated after exposure and before undue traction, clamping and ligation.

* From the Division of Surgery, Jackson Clinic. Submitted for publication, December 18, 1929.

Superficial cervical plexus block, produced by the foregoing technic, has been used in 300 thyroidectomies at the Jackson Clinic with entire satisfaction. It also has been used for many other operations on the neck within the anesthetized area.

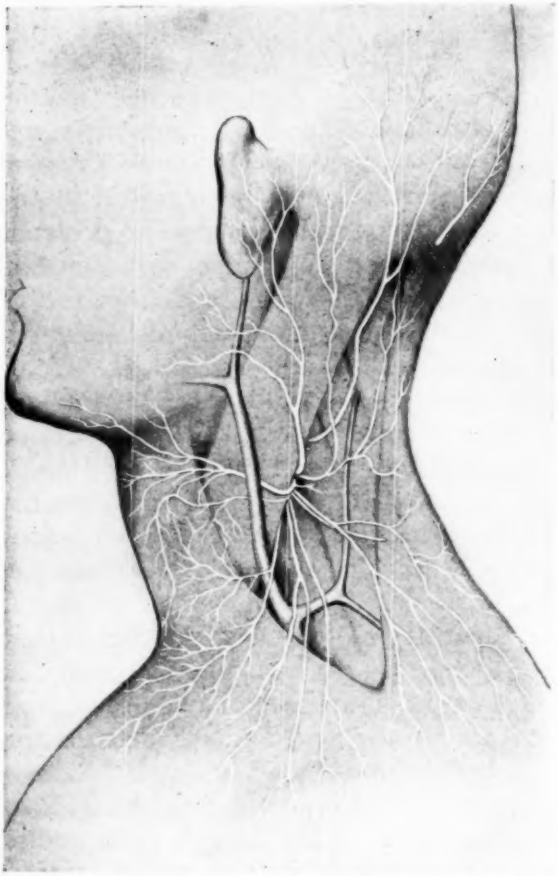

Fig. 4. Distribution of superficial cervical plexus. Shading indicates approximate area of anesthesia produced.

ADVANTAGES OF THE METHOD

1. The cooperation of a conscious patient is assured.
2. Undue vascular congestion is avoided.
3. Dissection of anatomically undisturbed tissues is easier than of edematous, infiltrated tissues.
4. Nerve block provides a complete anesthesia of a much wider and deeper area than is obtained by infiltration. Anesthesia of the lateral portions of the neck makes the patient more comfortable while lying on the operating table with the neck in hyperextension.

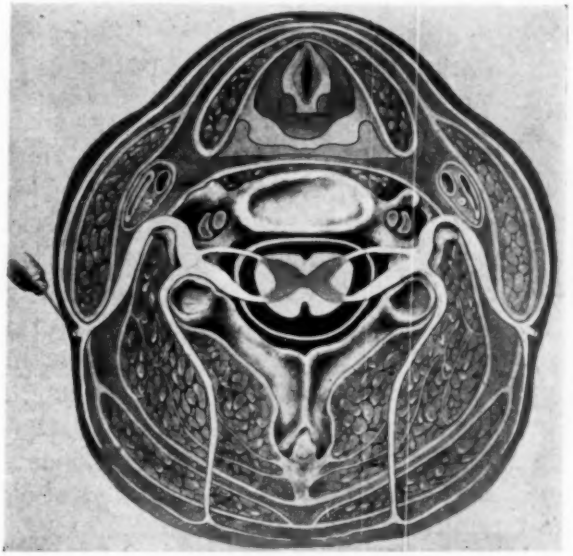

Fig. 5. Cross section of neck at level of fourth cervical vertebra showing point of injection. Anesthesia involves anterior three-fourths of neck. Deep anesthesia is not produced but it is unnecessary if preliminary pantopon-scopolamine is used.

5. Multiple needle punctures are avoided.
6. There is less danger of novocaine reaction from intravenous injection than with either infiltration or deep cervical plexus block.
7. Postoperative drainage is less profuse than with infiltration anesthesia.
8. The method is simple and easily mastered.

I wish to thank Dr. Arnold Jackson for his cooperation in the application of this technic to thyroidectomy.

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RECTAL ANESTHESIA

WITH TRIBROMETHYLALCOHOL*

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RECTAL anesthesia was first advocated by Pirogoff in 1847 with subsequent reintroductions that were received with little or no enthusiasm, excepting perhaps Gwathmey's method of ether in oil colonic anesthesia. This lack of popularity was largely due to the high incidence of postoperative rectal irritation and certainly to the uncertain depth of anesthesia that was effected. There has, however, been recently elaborated by Dusenberg and Willstatter, a new anesthetic compound, tribromethylalcohol, more popularly known as avertin.

Since the first presentation of this new anesthetic before the Berlin Surgical Society in 1925 by Butzengeiger, it has been used in over 250,000 cases that have been reported in the literature. This presentation will deal with the writer's personal experience covering a period of over three years, during which time the anesthetic was used in more than 600 cases. These cases will include a large number of anesthetics given during my association with Professors Sudech and Kummel, in the Surgical Clinic of the University of Hamburg, for a period of eighteen months, as well as several hundred given in this city since my original introduction of this anesthetic into the United States. It might be of interest to state that the first surgical procedure carried out under this anesthetic on this continent was performed by Dr. Joseph C. Beck of this city.

Tribromethylalcohol is a white crystalline substance with a melting point of about 79°C. to 80°C. It is readily soluble in water at 40°C. Its molecular structure is very labile and when heated above 45°C. it breaks down with a formation of a highly toxic and irritating substance, dibromacetaldehyde. It was the presence of the dibromacetaldehyde in improperly prepared solutions, that caused large numbers of rectal irritations to be reported in the first year or two of its use. The presence of this injurious substance in a solution may be detected by the appearance of a blue color when a few drops of Congo-red are added. It should be stated at this time, that one should never employ a solution when it has been tested and found unsatisfactory.

Tribromethylalcohol is very rapidly absorbed; in fact 80 per cent of the drug is absorbed during the first twenty minutes of anesthesia, at which time, it reaches a concentration of about 7 mg. per cent in the blood. In its passage through the body, it is detoxicated by combination with glycuronic acid and excreted in this form by the kidneys.

Its toxic dose is in the neighborhood of about 0.5 gm. per kilo body weight and its anesthetic dose is in the region of 0.15 gm. per kilo body weight with a consequent therapeutic index of about 2, which is higher than any other anesthetics that are available. Recent work has shown that the toxicity subsequent to the combined use of avertin and ether was less than when either one of these agents was used alone. It has no effect upon the conjunctiva, cornea or gastrointestinal tract. It causes no damage to any of the parenchymatous organs and, in animals that have been subjected to over 100 anesthetic inductions over a short period of time, no changes of the parenchymatous organs were demonstrable. Indeed several animals during this investigation became pregnant and gave birth to normal litters.

Anesthesia, as might be deduced from the very rapid absorption into the blood,

* Read by invitation before the Chicago Surgical Society, May 2, 1930.

occurs in a short period of time, as a rule in about seven minutes.

The writer's experience has been that unconsciousness may occur in as short a time as two minutes or an interval as long as twenty-five minutes may be required. This rapid induction is not attended by any excitation, the patient gradually becoming more drowsy and finally unconscious. The tendon and pupillary reflexes become weak and the pupils become contracted. However, this lack of reaction does not carry the same serious significance as it does with other anesthetics. The entire musculature of the body becomes relaxed. The pulse is little changed as to quality but its rate may be slightly increased. The systolic pressure falls about 10 to 20 mm. with little, if any change in the diastolic. There is a tendency for the restoration of a normal systolic pressure as the anesthetic progresses. The early fall may also be compensated by the use of ephedrine. Electrocardiagraphic studies during anesthesia showed no changes. The respirations are slower and shallower, but the respiratory efficiency is maintained by an increase in the tidal excursions. During anesthesia, an increase in the respiratory rate can be improved by carbon dioxide or lobeline.

PREPARATION AND ADMINISTRATION: PRELIMINARY MEDICATION

Any preliminary sedative or even none may be given. However, I have observed that morphine in larger doses than grain 1/6, causes a greater interference with the already depressed respiratory center and therefore advise caution in its use. A preliminary cleansing enema is advocated, but this may be omitted in abdominal conditions that preclude its use.

The anesthetic is slowly dissolved in a solution of water at 40°C. so as to make a 3 per cent solution. The dose varies from 0.05 to 0.18 gm. per kilo body weight, the larger dose used in children. It has been the practice to reduce the dose in the presence of large abdominal tumors, ascites, in kidney and pulmonary lesions, as well as in poor risks. As a rule a total dosage of 0.13 gm. per kilo body weight has given a satisfactory stage of anesthesia with pleasing surgical relaxation. In some instances an additional dose of 0.025 gm. per kilo was given when a patient failed to relax properly. A few cases would require the complementary use of a few drops of ether or a few whiffs of ethylene or any other anesthetic. Twenty per cent of my cases necessitated a complementary anesthetic as noted here. The patient had good surgical anesthesia which lasted from one and one-half to three hours, followed by a sleep of three to six hours. In addition to the rectal procedure, intravenous injection can also be used. Although I have used the intravenous method, I have not been impressed by any striking advantage. At this time, I might state that it is not my practice to give the entire dose at one time. The divided dose method that I have proposed, consists in giving half of the calculated dose and if sufficient anesthesia does not result, then I give half of the remaining dose and so continue giving half of the remaining dose until satisfactory anesthesia ensues. By this means, the additions of the anesthetics are smaller and smaller. The postoperative awakening is usually without incident and is comparable to awakening from an ordinary sleep. No nausea, vomiting or depression has been noted. About 10 per cent of my patients have complained of headache, which disappeared upon administration of pyramidon.

Broadly speaking, this anesthetic may be used in the entire domain of surgery and surgical obstetrics. Furthermore, it may be used in elderly patients, patients in debilitated states as well as in diabetes. It has been used in brain surgery, sinus surgery, pharyngeal operations, goiter, larynx, surgery of the chest and abdomen, as well as in gynecological, orthopedic and genitourinary procedures. Although various contraindications have been mentioned, only three have appealed to me.

Renal disease as a contraindication has been commented upon by various authors and since the kidney is the chief excretory organ of the anesthetic, caution is necessary in its use, although personally, I have performed nephrectomy with it.

Respiratory inefficiency is a definite contraindication, whether this be due to extensive pulmonary disease as tuberculoses, bronchiectasis or due to tracheal or laryngeal obstruction by tumor. This is due to the fact that the respiratory muscles are early inhibited by the anesthetic. I know of one fatality and two near fatalities due to the use of avertin in a case of laryngeal carcinoma, of extensive tuberculosis and of bronchiectasis respectively. Another contraindication is the presence of bleeding in the nasopharynx, as the protective pharyngeal and laryngeal reflexes are inhibited by the anesthetic. It is also contraindicated in an operation that may result in bleeding, such as tonsillectomy and adenoidectomy, nasopharyngeal tumors and sinus surgery. These contraindications are forcibly stressed and were brought to my attention by Drs. Joseph C. Beck and M. Reese Guttman.

MORTALITY

Although most authors have not reported any deaths from tribromethylalcohol, several have. Apparently the anesthetic risk that is intrinsic in this anesthesia is about 3 in 10,000. In the review of the literature, it is noted that the average death rates varies with the experience of the author. Those who report a series of cases of 1000 or more, show a death rate of 1.5 per 10,000. Those reporting in a series between 500 and 1000 show an average death rate of 3.5 per 10,000 and those reporting 100 or less, about 12 in 10,000. Furthermore, most or many of the deaths were not attended by post-mortem examinations and may be that the anesthetic was unjustly incriminated. The most complete survey of deaths following avertin anesthesia has been made by Kirschner, von Nordmann and Killian. Killian concluded that the anesthetic was the cause of death in half of the series that was reported by him. Kirschner commenting on the same cases concludes:

1. In some of these cases no post-mortem examinations were made and these could be ruled out as questionable deaths due to the anesthetic.

2. Many of these deaths occurred in the early period in the introduction of tribromethylalcohol, as a general anesthetic. Consequently lack of experience resulted in overdosage of patients with the resulting death.

3. The severity of operation may have been the cause of death.

4. It can be readily observed that accidents due to avertin have decreased with an increase in the knowledge in the action of this anesthetic. Glasmer has recently made a reply to the report made by Killian in regard to avertin deaths in which some of these cases could not and should not be associated with tribromethylalcohol as the cause.

Von Nordmann in a general statement believes that the percentage of mortality has been less than with other anesthetics.

CONCLUSIONS

It appears that this drug will probably occupy a highly important place in surgical anesthesia. Although the last word on tribromethylalcohol has not yet appeared, it approaches the ideal anesthetic more closely than any other at our present command.

AVERTIN BASAL ANESTHESIA

CLINICAL OBSERVATIONS

PRELIMINARY REPORT BASED UPON A STUDY OF 80 CASES*

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WASHINGTON, D. C.

ABOUT three years ago there was introduced abroad a new agent, known as avertin or tribromethanol, for the induction of general anesthesia by rectal administration. At present there is a wealth of German literature on the subject, and several papers have recently appeared in English medical journals.

The chemistry, pharmacology, dosage and technic of administration have been adequately discussed. The purpose of this paper is to report my experience in a limited number of cases in which approximately half the dosage necessary for surgical anesthesia was employed. The desired degree of anesthesia was attained by the supplemental use of inhalation anesthesia. Avertin should, in my opinion, be regarded solely as a basal anesthetic, the dosage being calculated for the individual patient so that a light narcosis, in itself harmless, is induced. This degree of narcosis assures to the patient practically all of the advantages that can be obtained by this method, while any disadvantages it may possess are minimized. Control of anesthesia is preserved by the supplemental use of the inhalation anesthesia. This permits the maintenance of any desired degree of anesthesia, which may be decreased at will to the point of the initial light narcosis. The best index as to the additional anesthesia required is the patient himself. Many of the undesirable characteristics of inhalation anesthesia are modified or eliminated by the use of this method of combined anesthesia.

The dosage of avertin used varied from 50 mg. to 100 mg. per kilo. of body weight, the average being 80 mg. Many factors influenced selection of the dosage. In extensive involvement of the liver or kidneys, obesity, acidosis, cachexia, diabetes, anemia, shock, hemorrhage and in other conditions rendering the patient a poor risk, avertin was used in less than the average doses, if at all. On the other hand, a somewhat larger dosage was required by children, young adults, persons of the sthenic muscular type, alcoholics, hypersensitive patients, and those suffering from acute abdominal conditions. In general, therefore, individuals that are usually difficult to anesthetize by any method, received the larger doses, while the poor risks, the elderly or feeble, and those with low resistance were given the small doses. Many other factors were considered, such as the amount of preliminary morphine medication, probably duration and extent of operation, the possibility of profound shock or hemorrhage ensuing, the skill of the operator. In fact, it was believed necessary to consider every eventuality, since pharmacologically avertin is a cerebral depressant. If exhaustion occurs from any cause, the depression of circulation and respiration produced by excessive doses of avertin becomes clinically evident; hence the use of a small dosage in order to remain well within the limits of safety.

The advantages of avertin anesthesia are many. The technic of administration is simple. There is an easy and pleasant stage of induction. The patient soon becomes drowsy and falls into a deep sleep with no unpleasant sensations; loss of consciousness is usually complete in ten minutes. The stage of recovery is equally calm, and many patients require little or no postoperative morphine medication, since the hypnotic effect of the drug wears off quite slowly.

Avertin is administered to the patient in his room, in which he goes to sleep and

* Submitted for publication, March 8, 1930.

later awakes, so that he remains unaware of the journey to and from the operating room. There is no stage of excitement or of muscular rigidity. The maximum narcotic effect is attained in from twenty to thirty minutes. Even when the dose is so small that consciousness is partially retained, the entire mental outlook is altered, apprehension is eliminated, and little if anything is remembered, because of the characteristic retrograde amnesia.

The individual variations in susceptibility are as pronounced with avertin as with other anesthetics. Withdrawal is impracticable. The degree of narcosis obtained with it determines the required amount of gas or ether, which may be augmented safely to the desired level of anesthesia, and later rapidly withdrawn. The combination of avertin with inhalation anesthesia seems to produce results unattainable with a single general anesthetic agent, and complies with Lundy's principle of a balanced anesthesia. It is possible to vary widely the percentage of oxygen in the gaseous mixture. For the more extensive intra-abdominal operations, ether was preferred to gas. In their influence upon the rate and amplitude of respiration, ether and avertin, in moderate amounts, are direct opponents, but both act in the same direction in securing anesthesia. With ethylene the respirations are likely to be slow and shallow; with nitrous oxide, more rapid and deeper; with ether, the rate and depth are also increased.

With patients having a tendency to cyanosis, not of mechanical origin, ether given by the drop method on the open mask acts as a respiratory stimulant, as does carbon dioxide and oxygen. Cyanosis does not necessarily indicate either an excessive degree of anesthesia or a mechanical obstruction. In rare instances, it may be due to direct action of avertin on the respiratory center and may be present with anesthesia insufficient for surgical purposes. Carbon dioxide and oxygen act well as a respiratory stimulant in light anesthesia and increase blood pressure, but are less effective after anesthesia deepens. The transient depression of respiration and circulation is also relieved by such operative manipulations as incision of skin, exploration of abdomen, etc. Most patients do as well without as with morphine, which acts similarly upon the respiratory center as avertin. For this reason, patients who receive both may occasionally manifest severe respiratory depression. Accordingly, avertin should not be given after heavy preliminary morphine medication. The systolic pressure may drop about 15 mm., then ascend slowly almost to its previous level, which is maintained unless influenced by other factors. In avertin narcosis the masseter muscles relax early and remain so for a long period. Salivation and bronchial secretions are inhibited.

When avertin is used as a basal anesthetic, the vomiting and respiratory spasm sometimes provoked by surgical procedures are absent. In fact, the patients cannot be made to vomit, the probable reason being that the function of the vomiting center is suspended. Recovery of the function of the vomiting center is gradual and too late after the operation to cause postoperative vomiting. However, if the nature of the operation or the condition of the patient is such as to exert a continuous stimulus upon the center, vomiting may recur after ten or twelve hours; this has happened after some intestinal operations, gastroenterostomy or cholecystectomy, and after operation for ruptured appendix with peritonitis, etc.

Some degree of muscular rigidity is often present when nitrous oxide is used, especially on closure of the abdomen, but with ether in small amounts relaxation is excellent. During an upper abdominal operation, if muscular rigidity and anoxemia occur due to traction or manipulation, no hesitancy need be felt in using ether to overcome this condition; it acts advantageously in deepening the respirations, relaxing the abdominal muscles and improving the patient's color.

I have observed in adults who are difficult to anesthetize (particularly men of muscular physique) and in one child of eleven years, a convulsive paroxysm upon withdrawl of the supplemental gas anesthetic. The clinical manifestations are those of a severe chill with rigidity of the abdominal muscles, opisthotonos, spastic contraction of the arms and clenching of the jaws. The attack is analogous to the recovery of the deep reflexes following other anesthetics and, while it is somewhat alarming, passes off in a short time and need not cause anxiety. It indicates that the patient is likely to recover from the anesthetic sooner than usual. With one exception, it was not noted when ether was used; in fact, a few breaths of ether on the open mask will relax the spasm. Rarely does a patient during recovery become excited; a hypodermic of morphine will quiet such a patient and enable him to secure several hours of sleep.

Clinical and pharmacological observations indicate that the period of anesthesia with avertin may be shortened, and blood pressure and respiration improved by the use of caffeine sodium benzoate. This drug has proved effective in interrupting the narcosis in laboratory animals, and at present seems the most promising for this purpose. It is probably useless to give less than 7½ to 15 grains of caffeine sodium benzoate to any patient requiring stimulation; it is safe to use large doses in such cases.

In moderately severe hyperthyroid types, the average dosage of 80 mg. per kilo appears to be well tolerated. In my opinion, its use is especially indicated in this and allied conditions. However, if the surgeon desires to test the phonation during the operation, the dosage of avertin should not exceed 60 mg. per kilo when supplemented with gas. This will usually secure the desired results. In ophthalmic surgery or whenever the patient must remain absolutely quiet, ether is preferable to gas as a supplemental anesthetic.

Patients who are difficult to anesthetize with gas, will respond more easily to avertin and gas; the administration of the latter may be varied within wide limits, without fear of vomiting or respiratory spasm. When avertin is supplemented with ether, the stage of excitement is absent, muscular rigidity is often so transient as to be hardly noticeable, and salivation or bronchial secretion fails to occur. A slow regular drop by the open method is sufficient in most cases. Usually, only a small quantity is necessary. When satisfactory relaxation has been secured, the ether may often be discontinued, or a small amount may again be administered just before closure of the abdomen. Relaxation, once obtained, lasts for an appreciable interval after the withdrawal of ether. If ether is to be used as the supplemental anesthetic, the dose of avertin may generally be reduced.

During the stage of recovery, which may last from one to three hours, the patient should be watched continuously by an attendant. As mentioned before, the masseter muscles are relaxed, the tongue and jaw dropped, and the pharyngeal reflexes diminished; failure to insure an open airway at all times may result in asphyxia. To prevent respiratory difficulty from mechanical obstruction, an airway may be inserted as soon as the pharyngeal reflex is abolished, and left in place during operation and the postoperative period.

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AVERTIN ANESTHESIA IN OBSTETRICS*

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TRIBROMETHYLALCOHOL or avertin, which has had wide usage abroad in surgical cases is now available for obstetric work in America. Being a rectal anesthetic it obviously has many advantages.

Avertin is a white crystalline powder which is readily soluble in water at a temperature of 104°F. at which temperature the solution should be maintained if possible. Light and air must also be excluded.

Absorption by the bowel is quite rapid. Eighty per cent of the drug is taken up in the first twenty minutes (Straub). In fact the chemical imbibition is much faster than the water in which it is dissolved. This circumstance is of great value in the case of ignorant patients who have a tendency to expel the fluid.

Elimination occurs through the kidneys by combination with glycuronic acid and for this reason it seems wise at present to avoid the use of avertin where the kidneys are damaged.

Toxicity need not be feared until about 3½ times the therapeutic dosage is exhibited so the latitude of safety is adequate. In combination with ether in the proportion of 1:1 or of 2:1 the anesthetic effect of both is increased and the lethal danger diminished.

The drug is dissolved in water at a temperature of 104°F. so as to make a 3 per cent solution. Hertzberg recommends a gum acacia solution as less irritating to the bowel. The temperature must not rise above 104°F. or the substance will decompose and liberate dibromacetaldehyde which is markedly irritating to the intestine and often destructive. Each usage requires fresh preparation therefore and each preparation must be carefully tested by adding 2 minims of a 1:1000 solution of Congo-red to every 5 c.c. of avertin. If the color is a clear orange red the solution is right. If it *turns blue*, free hydrobromic acid is present and the *mixture must be discarded.*

In our 10 cases 7 women were multiparas and 3 primiparas. Two of the labors were induced.

The dosage for anesthesia ranges from 0.1 gm. to 0.15 gm. per kilo of body weight. In our trials at the Wesley Maternity we used only .05 to .06 gm. per kilo of body weight and so obtained a narcosis in place of an anesthesia.

The administration was begun in our service when the dilatation was practically complete. The technic requires the introduction of a tube into the rectum above the advancing head, and through this the fluid is passed to the colon. Gravity is usually sufficient if the container is high but in some instances the head occludes the tube by pressure and a piston syringe is required.

The effect of the drug is said to begin in fifteen minutes and last for two hours. In our women the effect was evident in fifteen minutes and the average duration was one hour and fifty minutes, for 9 of the cases. One woman had 2 injections and the duration of the narcosis was four hours and thirty minutes.

The results of the narcosis in general were excellent. One patient got no relief. Nine women had no recollection of pain though in 2 cases the fluid was partially expelled. One woman stated that she felt as if a fish was sliding out of her. No preliminary excitement was observed and the awakening was as gentle as from a normal sleep. No headache or vomiting followed the narcosis.

During the narcotic period the pulse varied from 2 to 8 beats, the blood pressure shifted from 5 to 10 points and the respiration from 2 to 4 excursions in observations

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made at intervals of fifteen minutes. None of these changes was greater than one may find in normal labors from uterine activity alone.

In 3 instances the pains were slowed up somewhat but in no case were the contractions seriously affected or the evolution of the third stage influenced. In 2 of the labors 15 drops of ether were given as the head passed the perineum and in another the same amount was administered for the perineal repair.

Nine of the babes cried lustily as soon as delivered. The tenth patient, with a history of no heart tones on prenatal examination, delivered a macerated fetus.

In one woman there was a slight excess of mucus expelled from the bowel a few hours after delivery.

The observers of these cases are ready to believe that the absorption of the avertin will definitely mitigate the pains of labor in most instances, that used in narcotic doses it interferes but very slightly with the contractions and that it does not appear to pass over to the baby. From so small a number of cases no opinion can be final but the impression given in the clinic is that the drug is easy to use and with ordinary care as a basic anesthetic it is safe for the mother and will give great relief to those high-strung women who have strong contractions which they retard by fear and resistance.

TRIBROMETHYL ALCOHOL IN OTOLARYNGOLOGY*

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FEW specialities can have less reason than the otolaryngological to be satisfied with their methods of anesthesia. In 1925[1] I reviewed the methods of local and general anesthesia, emphasized their shortcomings and made a plea for rectal anesthesia in major surgical procedures about the head and neck as a means of placing anesthetic methods on a more accurate, rational and convenient basis. The justification for the employment of rectal methods of administration of anesthetic agents in our speciality is based upon the fact that we would minimize the manipulations of too many hands in an already small operative field and thereby not transgress the rigidly aseptic technic which many of our procedures demand. Since anesthesia is never likely to become an exact science, there is a great need for a form of rectal anesthesia on an agreed basis that will yield uniformly good results which will be comparable wherever obtained.

In our specialty, whenever anesthesia is mentioned, whether it be local or general, the question regarding both operative and postoperative complications is the paramount issue. Local anesthesia has been the choice of practically all rhinologists mainly because of the simplicity of administration and because of a possible greater margin of safety. In recent years, however, one is forcibly struck by the numerous reports in the literature of the toxic effects of the various local anesthetic agents, with the resultant fact that one must of necessity feel the uncertainty regarding this possible margin of safety. It is commonly accepted by all that general anesthesia used for operations about the nose and throat predisposes to the development of pulmonary complications but we also know that such complications can be secondary to general anesthesia when given for abdominal procedures or even following operations done under local anesthesia. It is generally conceded that infection may travel either by the lymphatic or the cardiovascular system or by direct extension into the tracheobronchial tree. Just at this time there are mainly two groups, one holding that the infection is embolic and the other that aspiration is the only possible way. Both schools of thought offer facts to substantiate their particular side of the question. It is not the object of this paper to discuss the pros and cons of either side, the point being relative to the uncertainty of the so-called perfected methods of local and general anesthesia.

There is no doubt that anesthesia, properly conducted, is distinctly a science, and as such should occupy an important place as a specialty in this broad field of medicine. Therefore, we would say that complications and mortality rates are not always an indication of the toxic or harmful effects of the anesthetic agent used; but by careful analysis in many instances one would find causative factors in a lack of the fundamental knowledge concerning indications and technic of administration. Then, too, such factors as operative risk, with reference to the individual patient, operative technic, and postoperative care are often forgotten and yet are fundamental in increasing the coefficient of safety of any anesthetic agent. Too often are methods thrown into discard because of improper application or lack of attention to the finer details of technic.

In 1923[2] I published a preliminary report on the method of synergistic analgesia as

[1] LEDERER, F. L. (with Beck & Pollock) Further report on synergistic analgesia. *Laryngoscope*, 35: 181–199, 1925.

[2] LEDERER, F. L. Synergistic analgesia. AM. J. SURG., 38: 80–88, 1924.

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proposed by Gwathmey, and later, in 1925, reported on another larger series of cases an improved technic of administration of this mode of rectal analgesia. The shortcomings of the synergistic method are only too apparent; namely the uncertainty of dosage, lack of uniform results and disconcerting sequelae. It is not unusual therefore that our interest should have been aroused when our attention was called to tribromethyl alcohol as an anesthetic agent. During the past year we have been working with this preparation known commercially as avertin. While this preparation was at first recommended to us as a basal anesthetic, we have been engaged in an extensive study of many cases to establish the dosage as a surgical anesthetic. As a basal anesthetic, the noticeable fact has been the small amounts of ether or other supplementary anesthetic agents that were required to induce muscular relaxation. We find that in our surgical procedures about the head and neck and especially the upper respiratory tract there is a distinct advantage to this form of anesthesia. Moreover, rectal anesthesia is definitely indicated in surgical cases wherein the patient is suffering from respiratory embarrassment (except of an obstructive character) or where the amount of absorption of anesthetic agents must of necessity be limited because of lung, heart or kidney lesions.

It is not the object of this paper to analyze critically and differentiate the various anesthetic agents on the basis of merit but rather to stress the value of this type of anesthesia in our field as one of the valuable adjuncts in the work. In our practice rectal anesthesia has always been popular and tribromethyl alcohol has proved itself practically easily administered and efficient. We would not be so dogmatic as to say its use is not the least bit fraught with danger but attention to the small almost insignificant details certainly will minimize any mishaps. I mention this merely because one sees such mishaps reported in the literature for which the anesthetic agent in most instances has been blamed, whereas the fault often lies with the other factor already mentioned. The use of any drug, even ether, was not meant for the tyro or inexperienced anesthetist and therefore it was our desire to proceed with our observations on a carefully controlled scientific basis.

Our technic of preparation of tribromethyl alcohol is the standard method recommended by other clinicians who have been working in this field and is summarized as follows:

Preparation of the Patient: Accurate weight (in kilograms) is obtained for the purpose of governing the dosage. Laxative or enema; sedative such as veronal, the night before to insure rest.

Preoperative: In cases where patients are of a nervous disposition or where difficulty is anticipated, morphine sulphate ¼ grain is given about two hours before the administration of tribromethyl alcohol.

Dosage: Given according to the patient's body weight (in kilograms) and according to the general condition, 125 mg. per kilo being the average dosage which was found to give the best results. In children the dosage was raised to the same amount per kilo of body weight because 100 mg. was found to be insufficient.

Preparation of the Solution: One c.c. of the avertin fluid equals 1 gm. of tribromethyl alcohol. Measure the dose of the fluid with a pipette graduated in tenths of a cubic centimeter. Heat the amount of distilled water necessary to make a 3 per cent solution to 40°C. (104°F.). Add the avertin fluid, dissolve by vigorously agitating and make sure that the material is actually in solution and not in suspension. Furthermore the mixture is tested by placing 1 or 2 c.c. into a test tube and adding two drops of 1:1000 aqueous solution of congo red; the resulting color under normal conditions being a clear orange red. If a change of color to blue occurs the presence of a free dibromi-acid alcohol is indicated and therefore the solution should not be employed as it is decomposed. Severe

irritation to the rectal mucosa results from a decomposed solution.

Administration: The injection of the 3 per cent tribromethyl alcohol solution at body heat is given as a retention enema either by gravity or gentle syringe pressure with the patient over on his left side, taking about five minutes for its introduction. Narcosis begins with drowsiness and takes place in from five to ten minutes. Suitable environment in a quiet and darkened room is desirable; and wherever possible, in the patient's own room.

Anesthesia: The patient is surgically anesthetized in from fifteen to thirty minutes and should be transported to the operating room with the least possible manipulation.

Supplementary Anesthesia: In some instances where the patient does not seem to be sufficiently anesthetized small doses of inhalation anesthetics may be indicated. It must be borne in mind that very little supplementary inhalation anesthesia is necessary to hold these patients surgically asleep. In some cases topical application or infiltration of local anesthetics is sufficient to supplement avertin as a basal anesthetic. We have not employed supplementary doses of avertin believing it to be an uncontrollable factor.

Postoperative: The noticeable factor has been the few cases wherein it was necessary to use postoperative analgesics. The time of sleep varied from a few hours to ten hours with a secondary sleep carrying the patient comfortably through the night. We have at the completion of our operative procedures often washed out the rectum, this despite the fact that we know the majority of the drug has been absorbed.

We do not feel that in this form of anesthesia we have replaced either the anesthetist or the nurse. The patient is to be watched closely especially as to the dropping of the jaw, there being such complete relaxation. The respiration is slower and more superficial, and in some instances the skin assumes a clammy appearance. In the majority of our cases the color has been normal throughout and only in cases of marked laryngeal obstruction have we noted cyanosis. This difficulty arises mainly because the glottis is narrowed and with the respiration slower and shallower the bellows action of the lungs is insufficient to force air through this chink.

Occasionally patients have complained of pain during operations or remonstrated in one way or another but upon awakening in answer to questions would recall nothing relative to pain or to conversation that took place. Perhaps the best reccommendation for an anesthetic is the patient's own acceptance or reaction to this form, and this is especially true in cases where patients have previously experienced different types of anesthesia. In a number of instances patients have stated to us that this anesthesia was the most tranquil they have ever experienced; moreover, in several patients we had known them to be poor subjects to every other form that was ever tried.

TYPICAL AVERTIN RECORD

Case 15 Date Sept. 17, 1929

Patient: Wm. M. Age, 19. Weight 62.4K. Sex Male
Diagnosis: Chronic Suppuration of left maxillary sinus
Preoperative Medication: Morphine Sulphate ¼ gr.
Amount of Avertin: 8 Gram. Amount of Water 268 c.c.
Time of Injection: 1:35.–1:40. P.M. Time Beginning Narcosis 1:55 P.M.

Time			
1:30 P.M.	Pulse 98.	Resp. 24	B.P. 150/90 P.M.
2:45 P.M.	95	24	150/90 P.M.
3:00 P.M.	95	24	150/85 P.M.
3:15 P.M.	95	24	142/85 P.M.
3:30 P.M.	98	28	150/85 P.M.
3:45 P.M.	85	26	142/90 P.M.

Time Operation begun: 2:55 P.M. Time Operation Ended 4:00 P.M.
Supplemental Anesthetic none
Time of Awakening: 10 P.M. Duration Secondary Sleep 8 hours
Character of Awakening As for normal sleep—didn't know he was operated

Blood	R.B.C.	W.B.C.	Differential P.	L.	M.
Before	6,848,000	16,600	65	28	7
1 hour after	6,720,000	14,000	66	30	4
24 hours after	6,540,000	16,200	68	26	6

Remarks: Left Radical Antrum (Luc-Caldwell) performed. Slight motions during operation but at no time were the motions sufficient to disturb the operator. No unusual bleeding.

Tribromethyl alcohol cannot be considered entirely experimental, since it has been used in Europe and in this country in more than 250,000 cases of surgical procedures of all kinds. The only contraindications that were known to us were certain diseases of the liver and rectum and advanced tuberculosis. Nevertheless we have been cautious in the selection of our cases excluding the elderly, debilitated and dehydrated individuals and patients with dyspnea due to laryngeal obstructions, We have used it in diabetics when the choice of the anesthetic left us in doubt. We have been fortunate to observe a number of cases which had previously responded very poorly to other anesthetic agents both local and general where avertin had proved its worth. Our cases have all been carefully studied and controlled by clinical and laboratory observations. Young children from the age of six, and adults up to the age of seventy, have comprised our series. It was quite noticeable that sleep was quickly and quietly induced, there being no stage of excitement, and while the respiration was shallow the entire period of sleep was tranquil. The patient awakes in a few hours and remembers nothing of the operation and the secondary sleep is quiet and seldom required analgesics for pain. After effects in the way of nausea, vomiting, headaches or abdominal discomforts are totally absent and we have never observed any outward effects due to rectal irritation. We are still at work perfecting the technic and it will be interesting to watch the unbiased reports of others as to the usefulness of tribromethyl alcohol as an anesthetic agent in our field. While we realize that there will be here and there reports of difficulties with this form of anesthesia we feel that the genuine pleasure of the results of the use of this agent warrants the lending of every effort to its use.

EFFECTS OF AVERTIN ON LIVER FUNCTION:

THE RATE OF SECRETION AND COMPOSITION OF THE URINE, THE REACTION, ALKALI RESERVE AND CONCENTRATION OF THE BLOOD AND THE BODY TEMPERATURE*

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AVERTIN (tribromethyl alcohol) was first prepared by Willstätter and Duisberg[1] in 1923, but it was not until 1927 that Eichholtz[2] first demonstrated its anesthetic properties. Since then avertin has been used widely in Germany: Spiegel[3] states that more than 80,000 cases have been reported to date. The pharmacological investigations of Eichholtz,[2,4] Straub,[5,6] Parsons,[7] Welsch[8] and many others concern the action of avertin on the circulation and respiration, the rate of absorption and excretion and its toxicity. Following upon our work on sodium amytal,[9] we have studied in a like manner the effects of avertin on liver and kidney function, the reaction, alkali reserve and concentration of the blood and the body temperature.

These observations were made on the dog and man. In the first experiments the dogs received 500 mg. of crystalline avertin per kilogram of body weight in 3 per cent aqueous solution per rectum. The solutions were always freshly prepared, were never heated above 40°C., and were always tested for decomposition products with congo red. The use of this dose of crystalline avertin in dogs gave us no trouble. Later, we began using avertin fluid (which is a 100 per cent solution of avertin in amylene hydrate) in the same dose and with the precautions mentioned. With this preparation, in 3 cases out of every 5, within five to ten minutes after the rectal infusion there was complete cessation of respiration and the dogs became markedly cyanotic. The heart, however, would keep on beating for some time. Inasmuch as we wished to avoid cyanosis as much as possible and, of course, fatalities, in these cases air at a low pressure was administered by means of a rubber tube introduced into the trachea; by compression of the trachea about the tube from the outside the lungs could be expanded at will. By this means we were successful in a large number of cases in maintaining a good color, but even this procedure in a small number of instances proved unsuccessful and the animal died. In those cases in which there was respiratory depression with marked cyanosis but in which respiration did not cease entirely, artificial respiration was administered manually. We thought that the dogs might have been dehydrated, thus favoring unusually rapid absorption of the drug; to offset this, 100 c.c. of water by stomach tube for every 3 kg. of body weight was given from one half to two hours before the administration of avertin. This was tried in 3 cases without success. The dose was then reduced to 400 mg. per kilogram of body weight and although the respiratory depression was less marked, there was still trouble in maintaining a good color. It is evident, therefore, that avertin fluid is far more effective than the crystalline substance, that the recommended dose of 500 mg. per kilogram for the dog is altogether too high when avertin fluid is employed, and that the state of hydration of the tissues does not influence its toxicity.

Harnack and Meyer[10] have shown that

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amylene hydrate at first stimulates and then depresses the respiratory center. We have never noticed any respiratory stimulation when avertin fluid was used. On the contrary, we are convinced that the respiratory depression is more marked with the fluid than with the crystalline substance.

Table I

AVERTIN ON LIVER FUNCTION

Experiment No.	Dose per Kg., Mg.	Time Blood Withdrawn following Avertin Administration, Hours	Dye Retention, Per Cent
1	500	24	30
		48	10
		90	10
2	500	24	5
		48	5
3	500	24	15
		67	5
4	400	24	25
		48	10
		72	10
		114	5
5	500	48	5
		72	5
6	500	48	5
7	500	24	5
		48	5
8	500	24	5
		48	− 5
9	500	24	10
		48	−10
		72	5
10	500	24	−5
		48	−5
11	400	24	−10
		48	−10

Human

1. Male. 59.1 kg. Herniotomy. 100 mg. per kg. avertin fluid. Nitrous oxide and oxygen for 20 minutes. One-fourth grain morphine postoperatively. No dye retention in 24 hours.
2. Male. 48.6 kg. Herniotomy. 100 mg. per kg. avertin fluid. Nitrous oxide and oxygen for 30 minutes. No morphine before or after. No dye retention in 24 hours.

In man, 100 mg. per kilogram of body weight was the dose of avertin fluid employed in 3 cases. No untoward effects were noted.

LIVER FUNCTION

The method employed for testing the function of the liver was that of Rosenthal and White,[11] which depends upon the removal of bromosulphalein from the blood by the liver. The results are shown in Table I. In the dog, 11 observation were made. Nine received 500 mg. and two 400 mg. of avertin (crystalline substance or fluid) per kilogram of body weight. It will be seen that the drug produces slight and transient but no delayed liver damage. In only 3 cases was there more than 10 per cent dye retention after twenty-four hours. Normal animals show less than 5 per cent retention of dye. In 2 human cases (done at the Western Division of the Montreal General Hospital) there was no dye retention twenty-four hours after the administration of 100 mg. of avertin per kilogram of body weight.

The results show that so far as hepatic function is concerned, avertin compares well with amytal[9] and the inhalation anesthetics,[12,13] the damage produced to the liver being negligible.

RATE OF SECRETION AND COMPOSITION OF THE URINE

Five experiments were conducted on dogs with bladder fistulas according to a method devised in this laboratory.[14] The urine was collected as it was secreted, urea determined by the method of Stehle[15] and phosphorus by the method of Pregl.[16] Tables II and III are examples of the results obtained. In every instance the animal received 500 mg. of avertin per kilogram of body weight by rectum. Anuria always occurs immediately after its administration and lasts for a period varying between fifteen minutes and one hour, after which marked oliguria occurs. The absolute output of urea is always lessened for four

TABLE II

BLADDER FISTULA DOG NO. 1

Weight 7.7 kg.

11.00 A.M.—200 cc. water by stomach tube

Urine

Time	C.c. per Min.	Mg. Urea per Min.	Per Cent Urea	Mg. P per Min.	Per Cent P
2.30– 3.30	.160	5.246	3.279	.083	.0517
0.5 gm. per kg. avertin crystals in 2.5 per cent solution per rectum (3.85 gm. in 154 c.c. water). Anuria for 25 minutes.					
3.59– 4.59	.100	2.732	2.732	.091	.0909
4.59– 5.39	.215	5.100	2.372	.232	.1079
9.05– 9.55 (next day)	.182	7.794	4.283	.680	.3736
10.10–11.10	.057	4.320	7.624	.171	.3026
2.30– 3.30	.100	5.128	5.128	.178	.1783

to six hours following the administration of the drug. The percentage excretion, however, is usually increased or only slightly lessened. Within eighteen to twenty-four hours the absolute output is approximately normal and the percentage is much above the control figures.

TABLE III

BLADDER FISTULA DOG NO. 3

Weight 10.8 kg.

11.30 A.M.—200 c.c. H_2O by stomach tube

Urine

Time	C.c. per Min.	Mg. Urea per Min.	Per Cent Urea	Mg. P per Min.	Per Cent P	Remarks
3.15– 3.45	.643	7.482	1.163	.191	.0297	Marked respiratory depression following administration of avertin.
5.4 c.c. avertin fluid in 180 c.c. H_2O per rectum (500 mgs. 1 kg.). Anuria for 47 minutes.						
4.27– 5.27	.123	1.854	1.504	.149	.1209	
5.35– 6.35	.148	3.592	2.422	.160	.1076	
8.56– 9.26 (next day)	.253	7.335	2.895	.800	.3159	Air intratracheally for 1½ hours.
10 18–11.18	.081	5.040	6.171	.133	.1630	
3.45– 3.45	.095	5.165	5.436	.165	.1735	

Phosphoric acid excretion is generally increased, both in minute rate and percentage output. The maximum excretion of phosphoric acid takes place from six to twenty-four hours after the administration of avertin; in only one instance did this occur in the first two hours.

Two observations were made on man at the Western Division of the Montreal General Hospital. The bladder was emptied and washed the evening before the operation. The urine passed thereafter was kept and added to that obtained at the next catheterization, just before the administration of the drug. Catheterization was repeated shortly after the operation and again twenty-four hours later. Table IV gives examples of such a case. In a general manner, the results obtained resemble those obtained with dogs.

TABLE IV

MR. D. AGE FORTY-NINE. WEIGHT 59.1 KG.

Herniotomy

Urine

Period	C.c. per Min.	Mg. Urea per Min.	Mg. P per Min.
Control (12-hour sample).....	1.09	10.570	.5515
5.91 c.c. Avertin fluid in 200 c.c. water by rectum (100 mm. per km.)			
Anesthetic (2 hour sample).....	.30	3.012	.3618
Postanesthetic (22 hour sample).	.44	7.568	.7169

It is obvious that the anuria which always follows avertin administration must either imply kidney depression or be due to a fall in blood pressure. The use of bladder fistula dogs does not lend itself to simultaneous determinations of urine flow and of blood pressure; nevertheless, it is evident from the protocols that the kidney is unable to concentrate urea for a time as much as normally. There is no doubt that kidney function is more depressed with avertin than with amytal;[9] in this it resembles ether[17–19] but the depression is transient and the kidney soon recovers, usually within four to six hours.

The human cases received only one-fifth of the dose given to dogs. The results obtained indicate that there is no evidence of severe kidney depression, inasmuch as urea was fairly well concentrated during the anesthetic period.

As has been found in the case of amytal, avertin produces blood dilution in the great majority of the cases. This would ordinarily be expected to cause an increased

urine flow. It is probable that oliguria occurs, in spite of the hydremia, because of the kidney depression or as a result of the lowered blood pressure.

The increase in phosphoric output which occurs following the administration of amytal, ether and, as we have now shown, avertin, is (as in the case of the former two) probably involved in the acidosis now to be described.

THE REACTION AND ALKALI RESERVE OF THE BLOOD

The carbon dioxide combining power of the plasma was determined by the method of Van Slyke and Cullen[20] and the pH values by that of Dale and Evans.[21] Table v shows the results obtained. It will be seen that following the administration of avertin the blood bicarbonate increases slightly in most cases for half an hour and then falls below the control figure. In one-third of the cases it fell from the start, but never to a marked degree. In 6 out of 8 cases the hydrogen-ion concentration of the blood increased, the pH values falling 0.1 to 0.2 units. In one instance the pH remained unchanged and in another there was a slight decrease.

As we have noted previously, in the greater number of experiments there was marked depression or complete cessation of respiration, involving, doubtless, an increase in the carbon dioxide tension of the blood. This may have been compensated for by a migration of base into the blood, thus accounting for the slight increase in blood bicarbonate. As the breathing became more depressed and artificial aids to respiration were employed, a considerable amount of the carbon dioxide may have been blown off from the lungs, resulting in a return of base to the tissues. This would account for the later fall in blood bicarbonate below the control figures. Thus, it will be seen from Experiment 10, Table v, in which pure oxygen was administered intratracheally but in which no artificial respiration was employed, a good color was maintained throughout the experiment and there was little change in the bicarbonate content of the blood.

The results indicate, therefore, that avertin does not affect the carbon dioxide combining power of the plasma to any considerable extent, provided there is no marked respiratory depression and a good color is maintained throughout the period of anesthesia.

Our pH determinations, on the other hand, point to a mild acidosis in the great majority of cases of the order found with amytal and ether. Like the latter two, it is also associated with an increase in the phosphoric acid output and we think that here too the disturbance in phosphoric acid, and possibly lactic acid metabolism, may play a part in the acidosis.

Koehler, Brunquist and Loevenhart[22] have shown that anoxemia produces a more marked acidosis than has been observed in any other condition, and it is probable in the case of avertin that the profound degree of anoxemia due to the respiratory depression may play an important part in the production of the acidosis. Nevertheless, a careful study of our protocols will show that a mild degree of acidosis has occurred in those animals in which little or no cyanosis was present.

BLOOD CONCENTRATION

Blood solids were determined by weighing a small amount of blood, as drawn, before and after drying to constant weight at 110°C. Table iv includes 8 such experiments. In 6 out of the 8 cases, there was a definite degree of blood dilution, especially in those instances (Experiments 4 and 6) in which the dogs received water by mouth before the avertin administration. In most cases, after two hours there was a slight degree of blood concentration, which is in keeping with the observation that the dogs drink water freely after recovering from the effects of the anesthetic. In this respect, avertin resembles amytal, both drugs producing a slight hydremia. The blood concentration and marked thirst observed with avertin one

Table V

Experiment No.	Dog No.	Weight in Kg.	Water by Mouth	Dose of Avertin per Rectum	Remarks	Period, Hours	Blood Solids, Per Cent	pH	CO_2 Comb. Power of Plasma in Vols., Per Cent	Rectal Temp., °C.
1	B1	28.0	.....	14 c.c. avertin fluid in 466 c.c. water (500 mg. per kg.)	Respiratory cessation. Air intratracheally for 30 minutes	Control	22.76	....	44.8	38.7
						½	24.65	....	48.4	
						1	22.49	....	44.2	35.7
						2	23.64	....	41.0	36.5
2	B2	25.2	.....	12.6 c.c. avertin fluid in 420 c.c. water (500 mg. per kg.)	Resp. cessation. Air intratracheally for 1 hr. Dog stuporous for 2 days. Died in 3 days from bronchopneumonia	Control	21.27	7.50	50.9	39.3
						½	20.37	7.40	55.8	37.7
						1½	20.31	7.50	49.0	36.2
						2½	20.33	7.50	45.5	34.0
						6½	24.63	7.42	40.7	36.8
3	L6	11.4	.....	5.7 c.c. avertin fluid in 190 c.c. water (500 mg. per kg.)	.....	Control	18.62			
						½	17.02			
						1	17.28			
4	B3	16.0	500 c.c. 3½ hrs. before avertin	8.0 c.c. avertin fluid in 270 c.c. water (500 mg. per kg.)	Cyanotic. Resp. depression. Artificial resp.	Control	20.80	7.50	49.1	38.4
						½	17.98	7.39	50.6	37.3
						1¼	21.76	7.47	47.4	37.4
						2¼	21.30	7.50	47.6	38.2
5	B4	24.9	830 c.c. 35 min. before avertin	12.45 c.c. avertin fluid in 415 c.c. water (500 mg. per kg.)	Resp. depression. Art. resp. for 15 minutes	Control	.....	7.62	56.1	39.2
						½	.....	7.39	53.0	37.5
						1	.....	7.53	52.3	36.2
6	B5	13.9	450 c.c. 45 min. before avertin	6.95 c.c. avertin fluid in 225 c.c. water (500 mg. per kg.)	.....	Control	19.55	7.48	45.7	40.4
						¾	16.79	7.50	48.5	38.2
						2	19.13	7.54	41.5	40.0
7	B6	26.3	.....	11 gm. avertin crystals and 2.15 c.c. avertin fluid in 440 c.c. water (500 mg. per kg.)	.....	Control	23.95	7.50	49.9	
						½	20.67	7.40	48.3	
						1	21.22	7.50	46.5	
						2	22.25	7.52	45.9	
8	B7	23.9	.....	9.5 c.c. avertin fluid in 320 c.c. water (400 mg. per kg.)	Resp cessation with extreme cyanosis. Air intratracheally for 25 m.	Control	22.0	7.52	57.6	
						½	22.47	7.45	56.7	
						1	23.45	....	51.1	
9	B8	31.8	.....	12.72 c.c. avertin fluid in 420 c.c. water (400 mg. per kg.)	Some cyanosis but no resp. cessation	Control	.....	7.50	52.2	39.9
						½	.....	7.50	57.6	39.2
						1	.....	7.50	50.9	38.8
10	B9	26.0	.....	10.4 c.c. avertin fluid in 350 c.c. water (400 mg. per kg.)	Pure oxygen intratracheally. Good color throughout. No artificial resp.	Control	22.76	7.41	52.9	38.0
						½	20.77	7.32	53.2	36.7
						1	20.57	7.52	51.1	36.2

or two hours following its administration has not been noted with amytal.

BODY TEMPERATURE

Table IV includes 7 observations, although more were made. In every case, there is a definite fall in body temperature from 2° to 5°C. which is probably due to the general quiescence of the animal and the decreased body metabolism. It is interesting to note in this regard that Harnack and Meyer[10] have shown that amylene hydrate (the solvent for avertin in avertin fluid) produces a definite fall in body temperature, but unfortunately we were unable to make a comparative study of the body temperature following the administration of crystalline avertin and avertin fluid, inasmuch as we were unable to obtain the former when the problem presented itself.

SUMMARY

Avertin has very little action upon liver function as determined by the bromosulphalein test, comparing favorably in this respect with amytal and ether. It produces marked kidney depression in the dog for one or two hours, but much less so in man, probably because of the smaller dose employed. When there is little or no respiratory depression and a good color is maintained, the blood bicarbonate content is little affected. With definite respiratory depression, the blood bicarbonate increases, due, presumably, to the attraction of bases into the blood. The increase in the hydrogen-ion concentration of the blood is probably due to two factors, anoxemia and disturbed phosphoric-lactic acid metabolism. Hydremia, followed by a slight degree of blood concentration and a definite fall in body temperature, also occurs.

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ANGINA PECTORIS*

PARAVERTEBRAL ALCOHOL BLOCK FOR THE RELIEF OF PAIN

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SINCE the original suggestion of cervical sympathetectomy by Francois Franck and the first actual surgical interference for the relief of angina pectoris by Jonesco of Bucharest in 1916, surgeons have attempted to relieve the agonizing pain incident to cardiovascular disturbance. That the surgical attempts are based on insufficient and inadequate anatomical, physiological and pathological evidence is amply borne out by the great variety of surgical procedures attempted.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

Before reporting our procedure, a brief description of the cardioaortic afferent nervous system will be discussed. The method used is based upon the following anatomical and physiological facts. The cardiac plexus is brought into contact with the sympathetic system through three cardiac nerves, i.e., the superior, middle and inferior cervical cardiac nerves. These nerves originate from the superior, middle and inferior cervical ganglia. The right superior cervical cardiac nerve enters the deep cardiac plexus and gives a few branches to the anterior surface of the aorta. The left superior cervical cardiac nerve joins the superficial cardiac plexus. It is of importance to note that the superior cardiac nerve communicates freely with the middle cardiac nerve and with the superior cervical cardiac branch of the vagus. The middle cervical cardiac nerve arises from the middle cervical ganglia. Often this nerve and ganglion are entirely absent. Both the right and left middle cervical cardiac nerves end in the deep cardiac plexus. The middle cervical cardiac nerve inosculates in the neck with the superior cervical cardiac nerve and the inferior laryngeal nerve of the vagus.

The inferior cervical cardiac nerve arises from the inferior cervical ganglion and at times from the first thoracic ganglion. It inosculates with the middle cervical cardiac nerve and the inferior cardiac nerve. The lowest cardiac nerve terminates in the deep cardiac plexus. The vagus nerve also ends in the deep cardiac plexus. The nerves of the heart are derived from the cardiac plexus. These nerves pass down along the aorta and are distributed to the auricles. From there they accompany the coronary arteries along the auriculoventricular groove, forming the coronary plexus. From this plexus branches are given off to the ventricles. The ascending aorta has nerve fibers which are in relationship through the rami communicantes with the first six spinal thoracic segments. There is some question as to whether the afferent fibers of the inferior cardiac nerve pass to the fourth, fifth, sixth and seventh cervical nerves. There is some evidence to the contrary. First, clinically, it is rare for pain to appear over the dermatomic segments supplied by the fourth, fifth, sixth and seventh cervical roots. Embryologically there is also some evidence against this occurrence. Head showed that afferent fibers from the heart enter the upper cervical and thoracic segments, extending from the first to the seventh dorsal segments. Apparently in the development the fibers going to the lower cervical nerves are not developed from the inferior cardiac nerves. All three cardiac nerves convey motor impulses to the cardiac plexus. Ranson maintains that most or all of the constrictor fibers to the aorta and coronary vessels come through the superior cardiac nerve. The sensory afferent impulses from

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the middle and inferior cardiac nerves reach the spinal cord through the rami communicantes. They enter into the thoracic segments, extending from the first to the seventh segments. These sensory afferent fibers are finely myelinated. Edgeworth maintains that such fibers pass into the central nervous system by way of the rami communicantes into the upper thoracic segments.

The accompanying diagram (Fig. 1) is a representation of what is generally known and accepted concerning the anatomical and physiological connections of the cardiac nerves to the spinal cord. Hypothetical nerves, such as a special depressor nerve and the vertebral nerve and structures seen in comparative anatomical studies but not established for human beings, have been passed over lightly in this discussion. Since every conceivable combination of operations has been performed and since the beneficial results are far from constant, an explanation of the varying results may be offered. Careful examination of the diagrammatic representation of the nervous mechanism shows quite conclusively that not only are the cervical ganglia in union with one another, but also that the cardiac nerves inosculate with each other as well as with fibers of the vagus. It is quite evident that the removal of any combination of ganglia and cardiac nerves leaves other pathways for pain stimuli to proceed to the brain stem and cord. Even if one were bold enough to attempt in a human the extirpation of all of the cardiac nerves on both sides, together with both vagi (if it were possible), impulses from the cardiac plexus and aorta would still pass into the spinal cord by means of the rami communicantes through the aortic nerve. They would enter into the cord from the first to the seventh dorsal segments.

Since most of the experimental work has been done on lower animals and since the operations on man have shown no definite, constant, results, the following question arises: What are the pathways for cardiac pain? At present the answer is not known. We do know, however, that irrespective of the place of origin of painful stimuli and irrespective of the cardiac nerves through which they pass, they must ultimately pass into the spinal cord or brain stem to travel by way of the spinothalamic tracts to the thalamus and ultimately reach the sphere of consciousness.

The problem can be solved by ascertaining definitely this point of entrance of the pain conveying fibers. With this knowledge, a mechanical interruption of the continuity of these entering fibers would prevent the pain stimuli from entering the cord. Head and MacKenzie suggested that painful stimuli passed from the heart by means of sympathetic fibers to dorsal root ganglia. The pain was thus referred to the surface dermatomes supplied by the irritated dorsal root ganglia. Any method, therefore, that would indicate through which dorsal root ganglia the mass of pain stimuli are passing, would indicate the exact areas to apply surgical intervention in order to block this entrance of pain impulses into the spinal cord. Another neurophysiological conception is important. Cells in the dorsal root ganglia that are being bombarded are hyperirritable to external stimuli. If a dermatome supplied by an irritable dorsal root ganglion is scratched with a pin or irritated by heat, it will produce a greater sensory reaction than would a skin area supplied by a normal dorsal root ganglion. Based on the foregoing premises, careful protopathic and epicritic sensory tests are made so as to determine the dorsal root ganglia that are being bombarded by pain stimuli. The object, therefore, is to destroy the poorly myelinated afferent sensory fibers from the heart which are passing through the sympathetic cords to enter a dorsal root ganglia. This can be done by destroying either the dorsal root ganglia or the afferent sensory, poorly myelinated fibers running in the sympathetic cords.

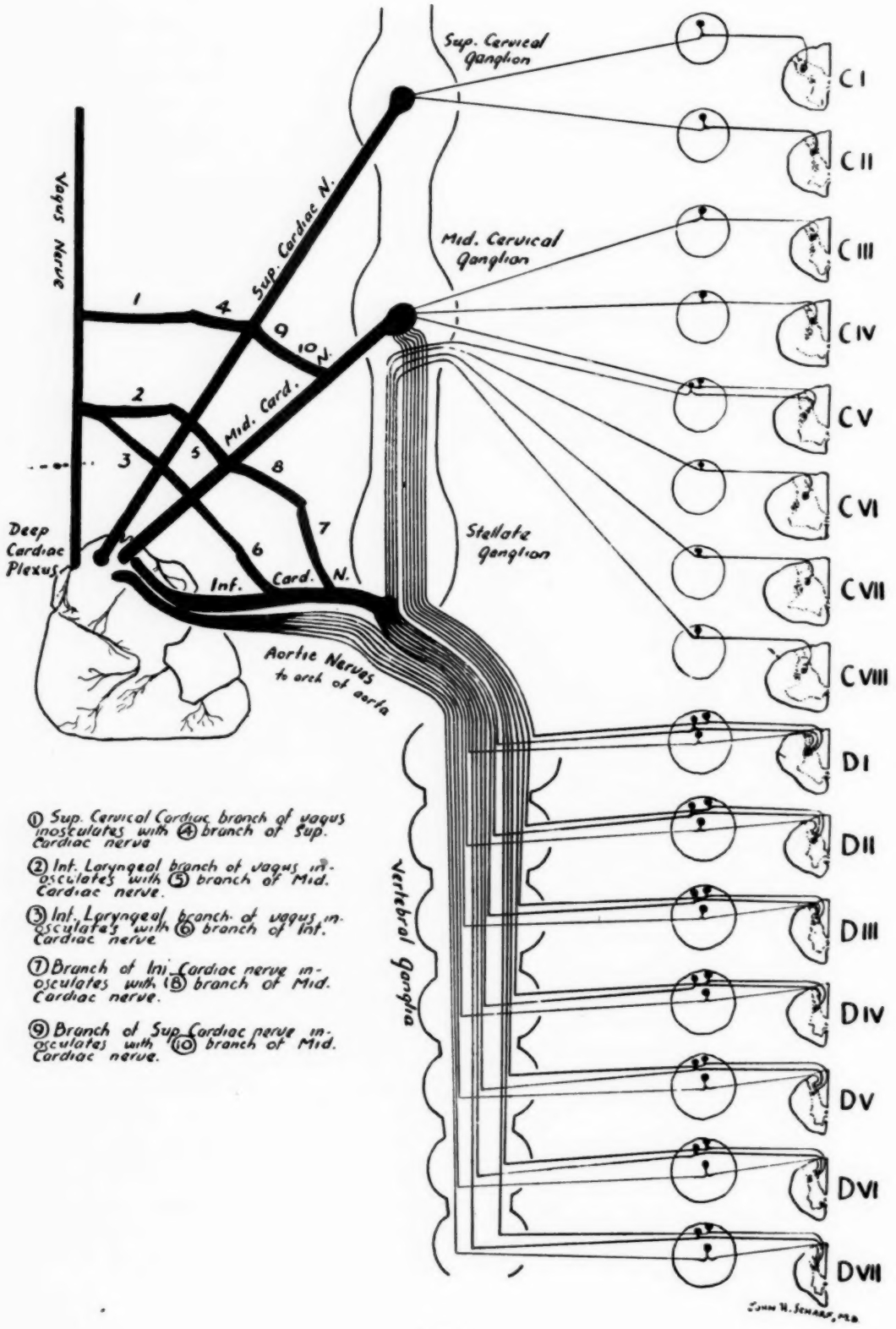
Sup. Cervical Ganglion
Mid. Cervical Ganglion
Stellate Ganglion
Vagus Nerve
Sup. Cardiac N.
Mid. Card.
Inf. Card. N.
Deep Cardiac Plexus
Aortic Nerves to arch of aorta
Vertebral Ganglia
C I
C II
C III
C IV
C V
C VI
C VII
C VIII
D I
D II
D III
D IV
D V
D VI
D VII
1 4 9 10
2 5 8
3 6 7
① Sup. Cervical Cardiac branch of vagus inosculates with Ⓐ branch of Sup. Cardiac nerve
② Inf. Laryngeal branch of vagus inosculates with Ⓑ branch of Mid. Cardiac nerve.
③ Inf. Laryngeal branch of vagus inosculates with Ⓒ branch of Inf. Cardiac nerve.
⑦ Branch of Inf. Cardiac nerve inosculates with Ⓑ branch of Mid. Cardiac nerve.
⑨ Branch of Sup. Cardiac nerve inosculates with ⑩ branch of Mid. Cardiac nerve.

FIG. 1.

EFFECT OF ALCOHOL INJECTED INTO NERVE TISSUE

Dogiel in his researches showed that the afferent sensory sympathetic fibers are finely myelinated. It is also known that these lightly myelinated afferent sensory sympathetic fibers arborize about certain cells in the dorsal root ganglia, i.e., Dogiel cells.

With the injection of alcohol into the dorsal root ganglia or into the sympathetic fibers in the vicinity of the dorsal root ganglia an intense Wallerian degeneration ensues.

In our cases we have used 3 to 5 c.c. of an 80 per cent to 85 per cent solution of alcohol paravertebrally in order to produce such destruction.

CLINICAL EVIDENCE CONCERNING THE PATHWAY OF CARDIAC PAIN AS ASCERTAINED BY THE SUBJECTIVE RADIATION

Irrespective of the place of origin of the painful stimuli which give rise to cardiac pain and of the nerves through which they pass, these impulses must ultimately pass into the spinal cord or brain stem to travel by way of the spinothalamic tracts in the spinal cord to the thalamus and thus ultimately reach the sphere of consciousness. Before entering the spinal cord, however, these pain impulses, as with any pain impulses, must first enter the dorsal root ganglia, so as to give rise to the phenomenon of referred pain. It is upon these basic physiologic principles that these subjective pain areas, as complained of by the patients, are explained. Of further interest are the observations, that the areas complained of are parts of the body surface relegated in nearly all of the cases to dermatomic segments that are supplied by those spinal nerves found between the eighth cervical and seventh thoracic segments. In a careful examination of the histories personally taken, as well as a perusal of the literature of many cases of pain due to angina pectoris, coronary disease and aortalgia, one is quite forcibly struck with the fact that the radiation of pain is relegated quite consistently to those areas of the body supplied by the eighth cervical down to the sixth or seventh dorsal (C VIII to D VII) nerves. These observations also revealed that any part or all of the chest may be subjectively referred to as the seat of the pain. Although it is true that at times the patients complain of pain in the back of the head (C I and II) or in the ear (C II) and at times in the lower jaw (trigeminal), yet it is worthy to note, that these two former sites are of rare occurrence while the last site is indeed a curiosity. A complaint of pain along the outside of the arm, which is supplied by the fourth, fifth, sixth and seventh cervical nerves is of such rare occurrence, that its actual existence is greatly to be doubted. In fact, anatomically, it is quite likely that no afferent sensory fibers of the inferior cardiac never pass through these four latter cervical nerves. Embryological studies also seem to support this conclusion. Therefore, from a clinical point of view as ascertained by the subjective complaints of the patients, we can logically say that the impulses which produced pain passed through dorsal root ganglia which supplied those dermatomic segments innervated by nerves emerging from between the eighth cervical and seventh dorsal spinal segments.

CLINICAL EVIDENCE CONCERNING THE PATHWAY OF CARDIAC PAIN AS ASCERTAINED BY THE NEUROLOGIC EXAMINATION (HEAD ZONES)

As stated, all sensory impulses which are conveyed by nerve fibers from an organ, must first enter into dorsal root ganglia before entering the spinal cord to be conveyed by the spinothalamic tracts to the sensorium. The spinothalamic fibers transmitting these stimuli arborize about cells in the dorsal root ganglia known as Dogiel cells. The constant bombardment of these somae by discharges coming from a diseased organ produce in these cells a state of hyperirritability. When a sensitive

dermatome, which is supplied by such an irritable cell, is roused by any physical agent, that is pin prick, heat, cold, painful response ensues. We thus see that this method of investigation is of great value in ferreting out those ganglia which are the recipients of the continuous stream of painful impulses from the diseased organ. Simply stated, this method reveals the pathway along which the painful influences are traversing so as to enter the spinal cord. Based upon these neurophysiologic facts, careful epicritic and protopathic tests were performed. In the 22 cases observed by the writer, definite sensory changes were observed over the skin. In all cases the protopathic skin tests clearly gave proof of the hypersensitiveness of the skin. Those zones of hyperirritability were limited to areas of the skin supplied by those peripheral nerves which emerge from between the eighth cervical down to the seventh thoracic spinal segments. Again, it is of value to note that the neurological examination failed to elicit Head zones over the back of the head (C I, II) or over the lower jaw (trigeminal nerve). The investigation also failed to reveal any hypersensitiveness of the skin to these tests over the radial aspect of the upper extremities (C IV–VII).

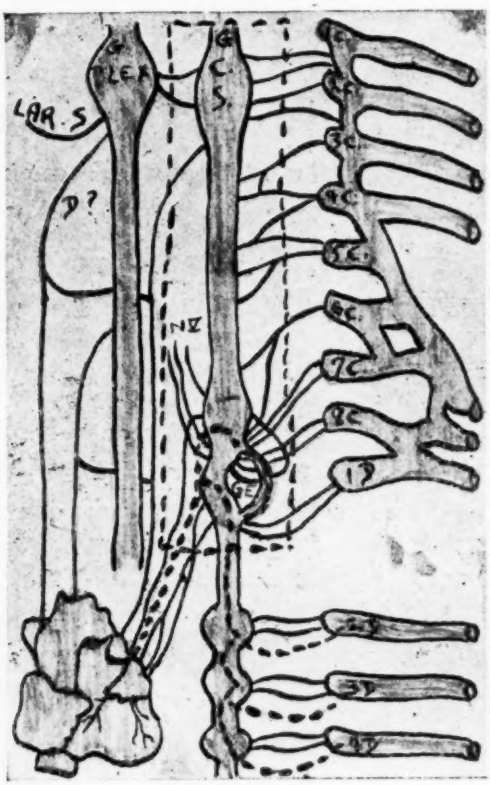

FIG. 2.

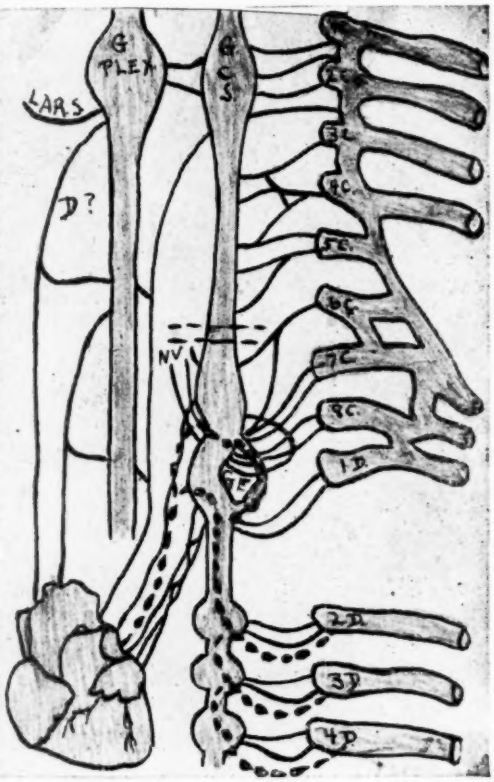

FIG. 3.

This method, therefore, also seems logically to suggest that the discharges of pain from the heart pass via those sympathetic fibers and dorsal root ganglia that are emerging between the eighth cervical and seventh dorsal (C VIII to D VII) spinal segments.

OPERATIVE EVIDENCES AS TO THE PATHWAY OF CARDIAC PAIN AS ASCERTAINED FROM THE VARIOUS PROCEDURES

In the review of the various operative measures instituted for the amelioration of the severe pain incident to cardiac disease, data were also elicited which clearly indicated what was not the pathway of pain from the heart. Nevertheless, these failures in the several surgical attempts to relieve the pain are of invaluable impor-

tance in indicating the correct pathways. The various surgical operations will be reviewed and discussed briefly, so that a clearer understanding may be obtained as to the significance of the information elicited, thus aiding in the disclosure of the correct pathway for cardiac pain.

1. *Method of Jonesco.* By this method the entire cervical chain, along with the first thoracic ganglion, was extirpated (Fig. 2). Danielopolu objected to this method. He contended that this operation severed the vasomotor fibers to the coronary arteries as well as the vasoconstrictor fibers to the lung. These objections were answered by Jonesco in a recent article. He asserted that physiologists, supported by extensive experimentation, are of the opinion that the sympathetics are vasoconstrictors. Hence the removal of the sympathetics does not impair the efficiency of the coronaries but, in fact, augments it.

2. *Method of Danielopolu and Hristide.* These operators sectioned the cervical sympathetic cord on the left side above the stellate ganglion (Fig. 3). Along with this section, the spinal ganglia of the spina nerves on the left side were injected with alcohol. At that time the operators were not ready as yet to report the value of this method.

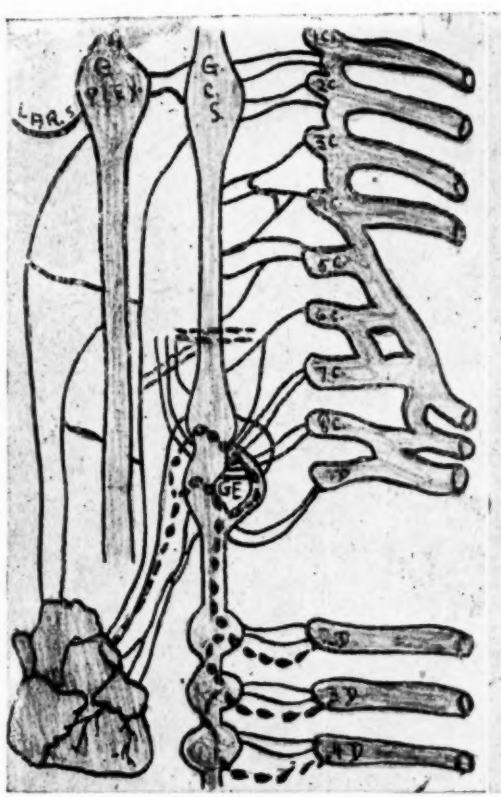

Fig. 4.

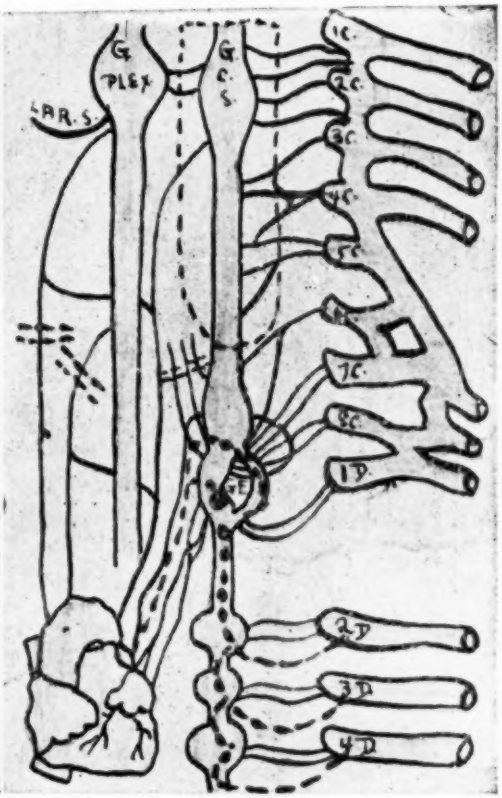

Fig. 5.

3. *Method of Danielopolu.* (A) On January 1, 1924, this surgeon reported that Gino Pieri of Bellino was the first to follow the operator's new method. He sectioned the cervical sympathetic chain above the stellate ganglion, together with the vertebral nerve, as well as a nerve which joins the superior cervical ganglion to the cranial nerves (Fig. 4). The immediate results were good. No reports as to the condition of the patient at a later date were given.

(B) In October, 1924, Danielopolu reported resection of the sympathetic cervical chain without removal of the inferior cervical ganglion and the first thoracic ganglion

(Fig. 5). In addition he sectioned the vertebral nerve and the branches of the vagus, which were about to enter the thorax.

thetics, together with the superior cardiac nerve on the left side. Hoffer in 4 cases of angina pectoris dissected the vagus nerve

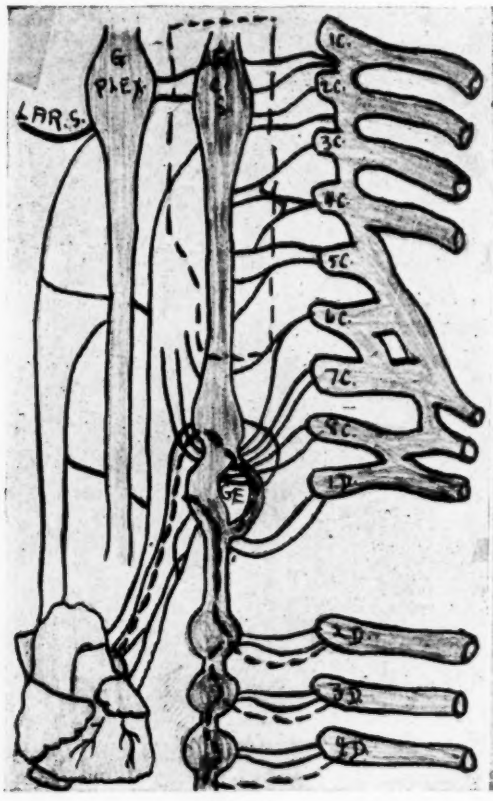

Fig. 6.

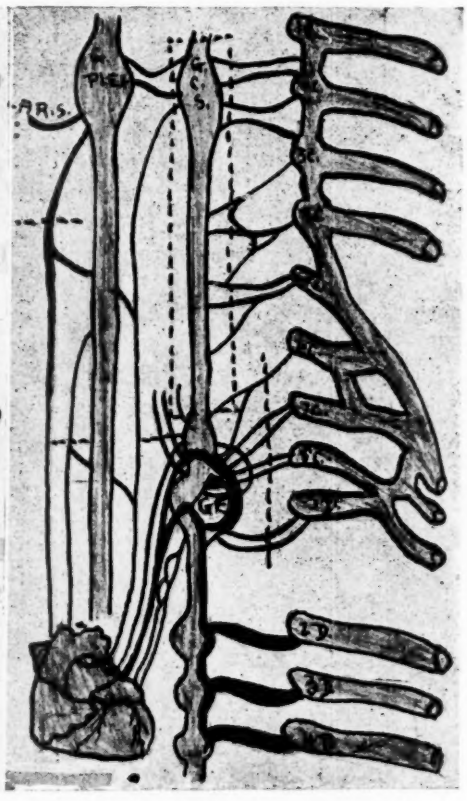

Fig. 7.

(c) In a less complete operation the superior and middle cervical ganglia were extirpated on one or both sides (Fig. 6). In January, 1925, Lilienthal reported 3 such cases with good results.

(d) In February, 1925, the following operation was performed by Danielopolu: the cervical sympathetic chain was resected. The inferior cervical ganglia, as well as the first thoracic ganglia, were left intact. The vertebral nerve was sectioned. All branches leaving the vagus to enter the thorax were severed. The rami communicantes, which joined the inferior cervical ganglion and the first thoracic ganglion to the last pair of cervical nerves, were severed (Fig. 7). In addition to these operations, Eppinger and Hoffer sectioned the so-called depressor nerve, while Coffey and Brown severed the cervical sympathetic ganglia.

without influencing the severity of the pain.

The resume of these various operations shows quite suggestively that if pain impulses do pass through the middle, superior cervical ganglia and vagus they do so in a very minor degree. These observations are quite supported by the animal experimentations to be later discussed as well as by the results obtained by the paravertebral alcohol nerve block.

Evidence as to the Pathway of Cardiac Pain Elicited by Means of the Paravertebral Block

This evidence is based upon 22 cases of my own together with 5 cases reported from the Massachusetts General Hospital and 16 cases of Mandl's.

In a recent paper from the Massachusetts General Hospital 5 additional cases

were reported in great detail in which the alcohol paravertebral alcohol block was used with admirable results. Mandl also reported 16 cases treated by this method with excellent results. This discussion, therefore, is based on a total of 43 cases, treated independently by three different operators. This method is of invaluable aid in the study of the route taken by these impulses which incite the perception of cardiac pain, in that we destroy nerve fibers and then observe what happens to the complaint of pain as personally expressed by those treated. The following theoretical principles are of value in understanding the paravertebral alcohol block as a method in studying the course of cardiac pain. As previously stated, the cardiac pain was referred subjectively to the surface of the body supplied by part or all of the nerves coming forth from between the eighth cervical down to the seventh thoracic nerves (C VIII to D VII, and again, as formerly set forth, these very same skin segments were the ones which were sensitive to skin tests. The conclusion was quite evident, that if these irritable ganglia or sympathetic fibers which came to the ganglia from the heart loaded with pain impulses, were destroyed, and if pain, as a result of the destruction, disappeared, the pathway of cardiac pain to a great extent would be solved. In light of the fact that an 80 per cent solution of alcohol destroys myelin and since the afferent sympathetic fibers are finely myelinated, a paravertebral alcohol block was performed, injecting each of the irritated ganglia. In all of the cases, the paravertebral injections were confined to those ganglia found between the eighth cervical and seventh thoracic (C VIII to D VII) spinal segments. The analysis of the 43 cases showed that those treated were mostly far advanced patients of heart disease, who suffered because of the persistent agonizing pain, that they all received a paravertebral alcohol injection into some or all of the dorsal root ganglia and rami communicantes which extended between the eighth cervical and seventh dorsal (C VIII to D VII) spinal segments, that, except for 5 cases, they were all relieved, in various degrees.

The results can be briefly summarized as follows:

1. Twenty-two patients suffering from attack of severe precordial pain, were treated by paravertebral injections of alcohol. Satisfactory relief was secured in every instance, except 2, i.e., 11 cases gave from 90 to 100 per cent relief, 7 cases gave from 50 to 85 per cent relief, and 4 cases were relieved from less than 50 per cent to nothing.

2. The alleviation of the pain following a single injection has usually lasted several months. One patient, who was reinjected after several months of relief, has again been made comfortable for a period of several months. This freedom from pain is still enjoyed.

Since the cardiac pain was relieved by the destruction by alcohol of the irritated ganglia found between the eighth cervical and seventh thoracic, we can reasonably say that the impulses of pain were intercepted by the alcoholic destruction of the nerves before they were able to enter the spinal cord, and since only nerves found between the eighth cervical and seventh thoracic were so destroyed, the conclusion naturally follows, that the pathway of pain is through those rami communicantes and dorsal-root ganglia found between the eighth and seventh dorsal (C VIII to D VII) spinal segments.

COMPLICATIONS AFTER INJECTIONS

In my own series of cases 5 of the patients complained of severe pain along the nerves injected. This persisted over a period extending from one to forty days. In some, the pain was sharp and paroxysmal while in others it was characterized as a dull ache. In all, however, the pain finally disappeared. There is no question in my mind that the pain is due to the chemical irritation of the alcohol inciting an alcoholic neuritis. This is borne out by

the evidence elicited by sensory tests over the skin.

In 1 case there developed a pneumothorax. I am unable to explain this. The suggestion that the needle accidently punctured the pleura and thus produced this complication does not seem convincing in light of the fact that there was no resulting pleurisy with effusion. It is almost inconceivable that alcohol could be introduced into the pleural cavity and no pleurisy with effusion result.

There were no deaths occurring on the operating table or immediately thereafter in spite of the fact that desperate cases were particularly chosen for treatment.

EVIDENCE ELICITED BY MEANS OF ANIMAL EXPERIMENTATION AS TO THE PATHWAY FOR CARDIAC PAIN

In a recent paper by D. Jonescu, experimental observations were made upon dogs and cats as to the course taken by discharges capable of producing cardiac pain. His experiments support the same conclusions as were arrived at through our clinical studies upon human beings. The following is a resume of the method used by the experimentor and the interpretation of the results as made by him. The experiment may be divided into four steps.

Step 1. Upon the pericardium or epicardium being pinched or pulled, or on the application of a 10 per cent solution of ammonium or barium chloride to the left ventricle or on making a similar chemical application to the adventitia of the left coronary artery or aorta, definite manifestations of pain reactions upon the part of the animals were seen, that is, marked movements of defence, increased respirations, rise in the blood pressure.

Step 2. The next step of the experiment was to sever on the left side the rami communicantes of the eighth cervical and the first thoracic (C VIII to D I) as well as the rami communicantes of the thoracic sympathetic chain down to the sixth ganglion. The first thoracic ganglion was not removed so as to permit its continuity with the cervical sympathetic chain and the vertebral nerve. With this section accomplished, there remained the following routes for the transmission of pain impulses from the left heart, the vagus with its depressor branch, the superior cardiac nerve, the cervical part of the sympathetic ganglionated chain, the vertebral nerve. Again the epicardium and pericardium, the left coronary artery and aorta were stimulated as was done in Step 1 and none of the reactions of pain as already described appeared in the animal. However, when the right ventricle was stimulated, a display of pain reactions was again elicited, though mild in nature. No evidences of pain resulted at all when the aorta was stimulated, even though the nerve structures were preserved on the right side.

Step 3. The next step was to resect on the right side the rami communicantes, which extended from the eighth cervical down to the sixth thoracic (C VIII to D VI). The application of the physical and chemical stimuli to the left or right ventricle, coronary artery or aorta roused no pain manifestations. This absence of pain is observed even though the vagus nerve, the depressor nerve, the superior cardiac nerve, the vertebral nerve and the cervical sympathetic chain are left unmolested.

Step 4. In other experiments as carried out in man, the same operator stimulated the cranial end of the sympathetic chain but no pain was produced.

Additional evidence was brought by Schittenhelm and Kappis to the effect, that the cervical sympathetic chain does not transport pain discharges from the heart and the aorta. They observed an attack of angina pectoris during an operation. They immediately injected novocaine into the trunk of the cervical sympathetic chain with no relief ensuing, while upon injecting the stellate ganglion, there was at once a suppression of the pain. In an earlier paper, D. Jonesco showed that the electrical stimulation of the cranial end of the vagus nerve as well as the depressor nerve or vertebral nerve, when found in

man, incited no pain reactions. Hoffer noticed in 4 cases of angina pectoris no influence upon the pain by severing the vagi. D. Jonesco pinched and pulled upon the vagus nerve without inducing pain evidences in the animals experimented upon. The experiments of Jonesco, together with the work of Hoffer, Schittenhelm and Kappis lead to the conclusion, that the impulses of pain pass from the heart through the stellate ganglion (C VIII and D I) as well as those rami communicantes that are found between the eighth cervical and sixth thoracic spinal segments.

SUMMARY

This paper is presented to correlate our previously observed clinical findings in patients complaining of severe cardiac pain with the information obtained by others through animal experimentation. The clinical observations showed, that subjectively, the pain was relegated to areas of the skin which were supplied by nerves arising between the eighth cervical and seventh thoracic spinal segments (C VIII to D VII). These very same skin areas to which the patients subjectively referred the pain showed them to be hypersensitive to protopathic tests (Head zones). These findings indicated that the pain impulses were passing through the rami communicantes and ganglia, which were to be found between the eighth cervical and seventh thoracic spinal segments (C VIII to D VII). The indifferent operative results ensuing from procedures upon the cervical sympathetic chain and other nerves in the neck indicated by their failure to ameliorate the pain, that the painful charges were not passing through these structures in their course to the sensorium. A review was made of 43 patients suffering from severe cardiac pain, who were treated by paravertebral block. The injections were confined to those rami communicantes found between the eighth cervical and seventh (C VIII to D VII) spinal segments. The gratifying results obtained seem to quite directly suggest that these rami communicantes and ganglia are the true conveying pathways of the pain impulses to the spinal cord so as to reach the spinothalamic tracts.

In a group of 22 cardiac patients suffering from attacks of severe precordial pain, who were treated by paravertebral alcohol injections of the dorsal root ganglia, prompt and satisfactory relief from pain was secured in all but 4 cases.

The freedom from pain following a single injection has usually lasted several months. In one patient, who was reinjected after four months of relief, there has been a second period of comfort lasting several months.

One case of pneumothorax followed the injection. Five cases developed an alcoholic neuritis which disappeared from one to forty days.

The resume of the animal experimentation supports the clinical observations. This showed clearly that the impulses were passing up through those rami communicantes and ganglia found between the eighth cervical and sixth thoracic. Such nerves as the depressor nerve and the vertebral nerve, rarely observed in humans, were stimulated in animals and failed to incite painful reactions. A perusal of all the data indicates quite clearly, that the future surgical procedures for the relief of cardiac pain must have their attention relegated to the rami communicantes found between the eighth cervical and seventh thoracic spinal segments (C VIII to D VII).

[For discussion see p. 105.]

ANGINA PECTORIS

TREATMENT BY PARAVERTEBRAL ALCOHOL INJECTION OR OPERATION BASED ON THE NEWER CONCEPTS OF CARDIAC INNERVATION*

JAMES C. WHITE, M.D.

BOSTON

I. SURGICAL ANATOMY OF THE CARDIAC NERVES

WHEN Swetlow[1] started to relieve the pain of angina pectoris by the paravertebral injection of alcohol, much of our present knowledge of cardiac innervation had not been worked out. The anatomy of the cardiac nerves is extremely important; first, because it shows us why cervical sympathectomy is so often a failure; second, because it holds out a distinct promise that with the perfection of our methods in attacking the upper dorsal sympathetic fibers, we shall be able to control all types of cardioaortic pain.

The fundamental anatomical facts about the sensory-motor nerve supply of the heart are as follows. Sympathetic afferent and efferent impulses enter and leave the spinal cord over the white communicant rami of the upper fifth to sixth dorsal segments (Fig. 1.) Below this level impulses go to the splanchnic system; above, in the neck, there are no white rami and therefore no connections between the sympathetic trunk and the central nervous system. The white rami leave the dorsal nerves just as the latter emerge from their intervertebral foramina. They then run a short distance below the pleura to the chain of sympathetic ganglia which lie on the anterolateral surface of the vertebrae. It is in this region that the cardiac impulses can be most effectively interrupted by alcohol block or surgical section, because the entire nerve supply to the heart lies concentrated here in the upper five to six pairs of white rami and the corresponding chain of dorsal sympathetic ganglia.

From this point on the pathways become infinitely diverse and complex. One part ascends to the stellate ganglion and the cervical trunk, to be relayed back to the heart over the superior, middle and inferior cardiac nerves. Between these fibers and the vagus there are numerous anastamoses. A second and very important group of postganglionic fibers leaves the upper dorsal sympathetic trunk, chiefly from the second, third, and fourth ganglia and run directly across the posterior mediastinum to the heart. The existence of these nerves has recently been proved in 2 ways: anatomically by Braeucker[2] and by Jonesco and Enarchesco,[3] who dissected them out; physiologically by Cannon, Lewis and Britton,[4] Brow and his co-workers,[5] and Spiegel.[6] Spiegel's experiments are of vital importance to us. He has demonstrated that dogs, in whom both cervical sympathetic trunks including the stellate ganglia had been removed, gave signs of pain when barium chloride was applied to the heart or when the ascending aorta was stretched. All signs of pain sensation disappeared after he removed the upper dorsal sympathetic ganglia.

The vagus nerve fortunately seems to carry no pain fibers, as there are numerous reported instances where it has been cut or directly injected with procaine without any result during an attack of angina occurring in the course of a cervical sympathectomy.

The direct pathways across the upper thorax were unknown when Jonesco devised his operation of removing the stellate ganglion and the cervical sympathetic trunk for angina pectoris. Today they are being constantly disregarded by surgeons who continue to use the cervical approach. I have gone into these anatomical details

*Read before the American Society of Regional Anesthesia, Stated Meeting, February 4, 1930.

in order to show that the logical point at which to block cardiac pain is the upper dorsal sympathetic trunk or its upper five

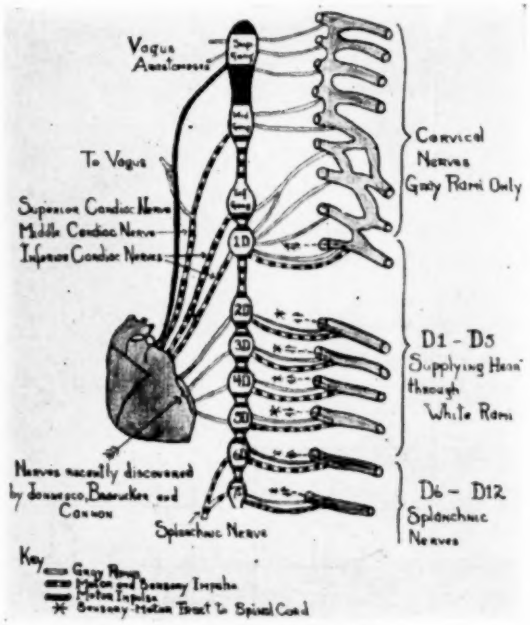

Fig. 1. Connection between central nervous system with cervicodorsal sympathetic trunk and nerves running from trunk to heart. Nerves described by Braeucker, Jonesco, Enarchesco and Cannon, connecting upper dorsal ganglia directly with heart, are sketched in outline.

or six rami communicantes. This is the neck of the bottle; all the sensory fibers entering the spinal cord from the heart are here nicely grouped and vulnerable to alcohol block or direct surgical removal. I have used both methods and can give the results in 21 cases which have been carefully followed over periods varying from three months up to three years.

II. CLINICAL CASES

1. *Indications and Contraindications:* All the patients in this series have first been submitted to a careful physical examination and thorough course of medical treatment by Dr. P. D. White. Only the ones who did not improve were later injected or operated on by Dr. W. J. Mixter or myself. At first we intervened only in cases where attacks were so severe that life was utterly unbearable. Then, as we found that blocking the cardiac nerves was a really safe procedure, we enlarged its indications to include all severe cases of patients who desired it, after they had had the pros and

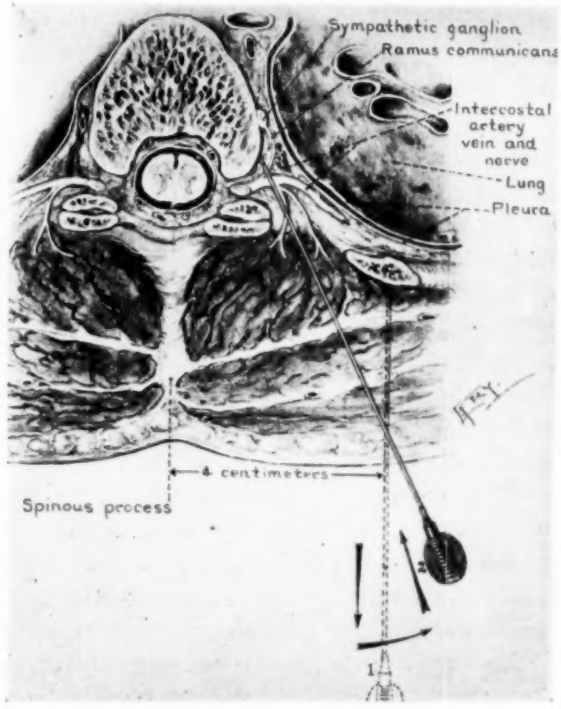

Fig. 2. Paravertebral dorsal block. Needle 1, after taking contact with inferior border of rib, is changed to position 2 and then advanced about 3 cm. further. It should strike body of vertebra close to intervertebral foramen. (From Labat's Textbook of Regional Anesthesia. Saunders.)

cons thoroughly explained to them. For patients who are able to afford complete invalidism and can be constantly cared for, we have been more reluctant to advise it than in poorer patients who are an impossible burden to their families if they are unable to walk about and do a little light work around the house.

There are very few contraindications to alcohol block. I think we should be on our guard against injection in the presence of any active sepsis, as the sterile areas of alcohol necrosis might become infected through the blood stream and set up a serious mediastinitis. Advanced cardiac decompensation would make injection dangerous, but under these circumstances angina is usually absent. Mild decompensation and previous attacks of coronary thrombosis are certainly not a contrain-

dication to injection as they are to operation, for we have injected 9 patients with such a history without bad results.

Danielopolu[7] believes that any interruption of the cardiac accelerator pathways which traverse the stellate ganglion and the inferior cardiac nerves is dangerous, but we have seen no evidence of this. Neither have we found any tendency for patients to overdo in the absence of the danger signal of pain, as claimed by MacKenzie.[8] Shortness of breath, peculiar sensations in the region of the heart without pain, or milder attacks on the right side have always given adequate warning.

2. *Method of Injection:* In the great majority of our cases, numerous anginal attacks have been occurring daily with the patient under observation in the ward. In these instances we have been able to determine accurately which rami carry the painful impulses to the sensorium by preliminary test injections of 5 c.c. of 1 per cent procaine-adrenalin solution, injected paravertebrally into each of the nerves supplying the skin areas of referred pain. These test injections have given pretty constant and complete relief for thirty-six hours; but we have never had results lasting weeks or months such as those reported by Mandl.[9] In the rare patients who cannot be counted upon to have 1 or more daily attacks, we have had to inject alcohol without this very useful information. We have not found Head zones of skin hyperesthesis to be as definite as reported by Swetlow and have not found them particularly useful in deciding which segments to inject.

Our method of injection has been fully described in 3 previous communications.[10] With some recent minor modifications, it consists in first infiltrating 2 c.c. of 2 per cent procaine around the trunks of the upper thoracic nerves as they emerge from the intervertebral foramina and give off their sympathetic rami. We are now using Labat's[11] second technic for inducing paravertebral anesthesia, Fig. 2. The needles are not moved and as soon as intercostal anesthesia develops, proving that they are accurately placed, we slowly inject 5 c.c. of 95 per cent alcohol into each.

3. *Cases Treated by Alcohol Injection:* Table 1 gives a summary of all the injected cases. One patient was injected bilaterally, so there are 19 injections to report in a series of 18 cases. Arteriosclerosis was the cause of cardiac pain in 15, syphilis in 3. The severity of the disease is shown by the fact that out of these 18 patients, 6 had angina at complete rest in bed and 7 had had previous attacks of coronary thrombosis. Most surgeons have felt that the latter condition is a definite contraindication. Of the 18 patients treated, nearly a half (47.4 per cent) have been completely or almost completely freed of their anginal attacks on the injected side and a quarter (26.3 per cent) have been very much improved. Thus three-quarters of the series were definitely successful. Of the remaining quarter, 10.5 per cent were only slightly relieved and 15.8 per cent were failures. Five of these patients have been able to return to work, Case IV as the driver of a heavy truck and Case XI as a mill foreman on his feet ten hours a day. Both were warned that they were overdoing, but felt that circumstances forced them to continue. The former was gradually compelled to lay off by the increasing severity of right-sided attacks, the latter by a cerebral hemorrhage.

There have been no fatalities nor major complications to date, the worst after-effects so far being 1 fairly severe and 2 milder attacks of pleural irritation from the alcohol. These passed off within twenty-four hours. The only troublesome factor has been a pretty constant skin irritation. Beginning usually about a week after injection, the skin anesthesia starts to wear off and is replaced by hyperesthesia. This intercostal neuritis lasts generally from two to six weeks. During this period the patient complains of sharp shooting pains around his chest and soreness of the skin. The hyperesthesia is borne without much complaint by the successful

TABLE I

PATIENTS TREATED BY THE PARAVERTEBRAL INJECTION OF ALCOHOL AT THE MASSACHUSETTS GENERAL HOSPITAL

Case	Age	Diagnosis	Treatment	Results	Degree Relieved, Per Cent	Duration	Status at Last Report
1	54	Syphilitic aortitis, aortic regurgitation hypertension, angina pectoris; confined to bed. Angina decubitus 15 attacks daily	Left $D_1 - D_5$ 2/19/27 Right $D_3 - D_7$ 3/20/28	Left-sided relief; development of right-sided pain, no relief	100 (left side) 0 (right side)	3 years	Up and about but unable to work; moderate attacks of right-sided pain
2	60	Hypertensive and arteriosclerotic heart disease, aortic regurgitation, angina pectoris, previous attack of coronary occlusion, slight congestive failure	Left $D_2 - D_6$ 5/16/27; reinjection $D_1 - D_3$ 6/28/27	Considerable relief; further relief	60	To death	Able to resume light work until sudden death, undoubtedly from coronary thrombosis or angina pectoris on Feb. 8, 1928; no autopsy
3	53	Arteriosclerotic heart disease, hypertension, angina pectoris at rest	Left $D_1 - D_5$ 6/9/27	Relief slight but definite; difficult to judge because of extreme nervousness	25	To death 2¼ years	Up and about, quietly active, appearing in good health but with moderate angina pectoris. Died of empyema
4	54	Moderate arteriosclerosis and enlarged heart; angina pectoris; incapacitated	Left $D_1 - D_5$ 7/22/27	Left-sided relief; mild right-sided attacks	100	To date 2½ years	In fair health, but still has right-sided angina pectoris (mild); resumed work as truck driver for three months, but is too short of breath now
5	56	Arteriosclerotic heart disease, hypertension, myocardial insufficiency, previous coronary thrombosis	Left $D_1 - D_5$ 8/12/27	Relief partial	40	To death 4 mos.	Died suddenly on Jan. 9, 1928, undoubtedly of coronary coronary thrombosis or angina pectoris; no autopsy
6	52	Hypertensive heart disease, aortic regurgitation, angina pectoris at rest	Left $D_1 - D_5$ 11/5/27	Complete relief at first: later slight recurrence	100	To date 2¼ years	Comfortable and able to do light work. 5mos.
7	58	Arteriosclerotic heart disease, hypertension angina pectoris	Right $D_1 - D_3$ 3/3/28	Considerable relief	65	To Aug. 1928 5 mos.	Fairly comfortable and has resumed light work
8	68	Arteriosclerotic heart disease, hypertension, angina pectoris, previous coronary thrombosis	Left $D_1 - D_5$ 4/17/28	Partial relief at first, then recurrence, judgment of case somewhat difficult because of nervousness	50	To death 10 mos.	Uncomfortable, angina pectoris daily but able to be quietly up and about. Died of coronary thrombosis
9	47	Hypertension, arteriosclerosis, coronary thrombosis, angina pectoris; confined to bed	Left $D_1 - D_5$ 9/4/25	Complete relief of attacks	100	To death 2 mos.	Died of myocardial failure with right-sided angina pectoris on November 4, 1928
10	51	Arteriosclerotic heart disease, coronary thrombosis, angina pectoris, morphinism	Left $D_1 - D_5$ 9/14/28	Relief of attacks	...	To death 3 weeks	Five days later another attack of coronary thrombosis; died October 4; died too soon to judge
11	56	Hypertensive and arteriosclerotic heart disease. Angina on exertion	Left $D_1 - D_3$ 6/25/29	Complete relief for 4 months. Slight recurrence 2 months ago	100 90	To date 7 mos.	Worked for 4 mos. Stroke 2 mos. ago. A few slight attacks since
12	57	Hypertensive and arteriosclerotic heart disease. Angina on exertion. Coronary thrombosis	Left $D_1 - D_4$ 10/6/29	Very much improved	90	To date 4 mos.	Returned to light work. Rare attacks
13	56	Arteriosclerotic heart disease plus coronary thrombosis. Angina on exertion	Left $D_1 - D_3$ 10/29/29	Complete relief	100	To date 3 mos.	Continues at practice of medicine
14	54	Arteriosclerotic heart disease, coronary thrombosis, decompensation, angina decubitus	Left $D_1 - D_4$ 10/24/29	Complete relief	100	?	Followed only two weeks
15	49	Arteriosclerotic heart disease, angina on any exertion	Left $D_1 - D_3$ 10/31/29	Much improved	75	To date 3 mos.	To return to work soon
16	57	Arteriosclerotic heart disease, angina on exertion	Left $D_1 - D_4$ 11/28/29	No relief	0	.....	Continues as before treatment
17	52	Syphilitic heart disease, aortitis, angina decubitus	Left $D_1 - D_4$ 11/18/29	No relief	0	.....	Continues as before treatment
18	50	Syphilitic heart disease. Aneurysm of ascending arch of aorta. Pain in upper right chest and neck	Right $D_1 - D_2$ 2/7/29	Complete relief	100	To death 3 mos.	Died of rupture of aneurysm

cases, although one patient told me that it was as bad as his angina for a week; but in the unsuccessful cases it is really annoying.

I see no way in which this reaction can be prevented, as the sympathetic rami are so short and the ganglia lie so close to the intercostal nerve trunks that there is no way of blocking the one without irritating the other. When 5 c.c. of alcohol are injected into the loose connective tissue between the pleura and the intervertebral foramen, an area of scar tissue about 1 cm. in diameter is produced (observed in the autopsy of Case XVIII and in experimental animals). The alcohol must therefore be deposited with considerable accuracy close to the intervertebral foramen. But unless the injection is made directly in to the nerve trunk itself, the nerve sheath is so impermeable that no more than a transitory peripheral anesthesia is produced. As this wears off, the intercostal nerves are bound to go through a period of hyperirritability; by the end of two months or less, normal function returns. In the case of the delicate sympathetic rami, however, the destructive action of the alcohol usually results in a permanent block. Thus 3 of our patients injected between two and three years ago still report complete relief on the injected side. Only 3 cases have shown any tendency to relapse and in 2 of these the attacks have remained mild in comparison to their former severity. The majority of our successful cases have shown other signs of sympathetic nerve block, e.g. Horner's syndrome, vasodilatation and cessation of perspiration in the arm. In Case XII after four months these changes are still as marked as in patients where we have resected the corresponding ganglia for Raynaud's disease.

Case XVIII is, to my knowledge, the first reported instance of blocking pain in aortic aneurysm. This patient had a huge dilatation of his ascending aorta involving the innominate artery as well. There was constant, severe, aching pain, involving the right upper thorax, neck and posterior scalp to the top of his head. When he coughed the pain was almost unbearable. The referred pain, therefore, spread over all the spinal segments from the third dorsal to the first cervical on the right side. As the cervical sympathetic trunk is connected with the spine only through the upper dorsal rami, I suspected that paravertebral injection in this region would block the entire area. A test infiltration of procaine into the two upper dorsal spaces on the right blocked the pain for thirty-six hours. Alcohol injected two days later gave complete relief for three months, when the man reentered the hospital because of an acute respiratory infection. He died suddenly of rupture of the aneurysm. Autopsy showed areas of dense scar tissue 1 cm. in diameter at the openings of the 2 upper dorsal intervertebral foramina, surrounding the communicant rami down to the sympathetic ganglia. The parietal pleura was densely adherent to the vertebrae, but the scar did not involve the wall of the aneurysm which was pressed against the spine at this point.

These findings show that alcohol block, when successfully performed, can interrupt the cardiac afferent pathways as effectively as direct operative division. But the cases reported here show that we have injected the alcohol into exactly the right spot in only a half of our cases and fairly accurately in 25 per cent more. Undoubtedly our technic can be improved, but I fear that on account of the depth of the rami and the small area sclerosed by the alcohol, we must always expect a moderate number of unsatisfactory results. However, even in our present state of imperfection, these results are definitely superior to those reported from cervical sympathectomy. The much greater safety of injection over operation is very much in its favor, which means that for the average patient with severe angina and a badly damaged heart, we must strive to perfect our technic and stick to injection. But in the exceptional case of the good surgical risk, we have begun to excise these same nerves by operation.

4. *Operated Cases:* On the basis of our present knowledge of cardiac pain here reported, resection of the upper dorsal sympathetic ganglia seems to be the logical form of surgical approach. I know of no instances in which it has been used in other clinics. In spite of the fact that it is still in its experimental stage and outside the topic of discussion for this meeting, I am including a brief résumé of 3 cases treated by this new operation. I do this because it has increased out knowledge of cardiac pain and because we are planning to use it in preference to injection in the rare anginal patient who we feel can withstand a more radical operative procedure.

Table II summarizes the essential details of these cases. All three appeared to be safe operative risks and were suffering from very frequent severe attacks of angina pectoris. In the cases of two young men, it was particularly important to restore them to some degree of economic independence. Preliminary paravertebral injection of procaine showed that blocking of the stellate and the second dorsal ganglia sufficed to stop the anginal attacks. These patients were operated upon by Dr. W. J. Mixter, Dr. A. W. Allen and myself. We first removed a small segment of the second rib, subperiosteally as reported by Adson[12] for interrupting the sympathetic innervation of the arm in Raynaud's disease.* The parietal pleura was then pushed away from the vertebral bodies until the sympathetic trunk came into view. It was then easy to excise the first dorsal portion of the stellate ganglion, the second, and in 2 cases the third dorsal ganglia. This extrapleural approach seemed to cause no shock and all 3 patients made good postoperative recoveries. Case II, on the eleventh day after operation suddenly developed a terrifically severe attack of right-sided precordial pain, from which he died in three hours. Autopsy showed total occlusion of the mouth of his left coronary artery and partial occlusion of the right. This was due to luetic aortitis and was not of recent origin. As there was no other apparent cause of death, it is impossible to say whether his death was a mere coincidence or a direct consequence of operation. If the latter, it is surprising that he should have done so well for ten days.

In all these cases the left-sided angina disappeared completely. It is interesting that all 3 had mild right-sided pain before operation, which was not influenced in any way by the unilateral operation. These right-sided attacks were just severe enough to constitute a good danger signal in Cases I and III. The former neglected his health completely, working hard as an insurance agent and sitting up late nights. After nine months he reentered the hospital with an acute respiratory infection and died suddenly of a severe attack of right-sided angina. Neither in his case nor in the second, was there any trace of pain on the left. The last patient is doing well after four months. She has slight attacks of right-sided pain, which warn her when she is overdoing, but do not prevent her from doing light housework and enjoying mild, social activities.

Table II

DORSAL GANGLIONECTOMIES IN ANGINA PECTORIS

Case	Age	Diagnosis	Operation	Results
1	18	Rheumatic heart disease. Aortic regurgitation. Up to 18 attacks of angina at rest daily. Severe on left, mild on right.	Resection $D_1 - D_2$ 2/5/29	Complete relief of left-sided pain. Return to active work. Died at nine months of right-sided attack
2	29	Syphilitic aortitis. Three to four daily severe attacks of left-sided angina.	Resection $D_1 - D_2$ 9/19/29	Good recovery and no more pain. Died suddenly on eleventh day with severe right-sided pain. Autopsy showed total occlusion of left coronary artery, 50 per cent occlusion of right coronary
3	57	Rheumatic and hypertensive heart disease. Severe angina on left, mild on right.	Resection $D_1 - D_2$ 10/1/29	Total relief on left. Still has mild right-sided attacks

*This operation was first proposed by A. K. Henry (*Irish J. of Med. Sc.* 5: 157, 1924), who worked out the procedure on cadavers and suggested its use in angina pectoris.

5. *Discussion:* From my experience with these cases, I have come to the conclusion that paravertebral injection of alcohol is the best treatment that has been developed for the average patient with severe angina pectoris. All of them have reported back to the Cardiac Clinic at frequent intervals and I have taken Dr. P. D. White's opinion of the degree of improvement following injection, in order to be sure of an impartial estimate. A summary of this data classified on a percentage basis, is given in Table III.

TABLE III

		Paravertebral Alcohol Block, Per Cent		Cervical Sympathectomies, Per Cent	
				Total	Partial
Number of injections or operations		19*		66	116
	per cent				
Relief	Good 100 to 90	47.4	73.7	58	53
	Good 90 to 50	26.3			
	Improved 50 to 25	10.5		13.4	22
	Failures 25 to 0	15.8		7.6	13.5
Deaths		0		21	7.5

* Two cases observed too short a time to be certain of result.

This shows that the results of injection are distinctly better than in the large series of cervical sympathectomies collected by Fontaine[13] and Cutler.[14] After removal of the upper cervical sympathetic trunk there is a 7.5 per cent chance of the patient's dying within the first four days; after the complete Jonesco operation, which includes the stellate ganglion, the chances are increased to 21 per cent. So far we have not been sorry that we have injected any patient. Furthermore, the average operated patient requires a hospitalization of nearly two weeks, while for the case treated by injection, three to five days are usually sufficient. In the face of these statistics, no cervical sympathectomy has been performed at the Massachusetts General Hospital during the past three years.

Injection has taught us that when the sympathetic rami of the upper thoracic nerves are successfully blocked, pain in the precordium and inner surface of the arm disappears on the injected side. This has happened temporarily in every instance following the use of procaine and in every case but one with alcohol, where complete skin anesthesia resulted. When the angina is bilateral, injection on the left has no effect on the attacks on the right. In regard to atypical anginal attacks in the epigastrium and neck, I have not had sufficient experience to make any positive statements. However, in Case XVIII, pain referred all over the cervical distribution was relieved when the upper thoracic rami were blocked. Once alcohol has failed, there is little more that can be done for the patient surgically, as attempts at reinjection in our hands have failed and operation would be rendered much too difficult by the scar tissue. It is for this reason that we are beginning to remove these nerves surgically in a few favorable cases where we are willing to take an additional risk in order to be surer of success.

SUMMARY

(1) Pain from the heart and ascending arch of the aorta is conveyed to the sympathetic trunk by postganglionic, unmyelinated fibers running in:

a. The superior, middle and inferior cardiac nerves to the correspounding cervical sympathetic ganglia.

b. Recently discovered nerves which run directly across the mediastinum from the posterior cardiac plexus to the upper dorsal sympathetic ganglia.

The painful stimuli are then carried to the spinal cord over preganglionic, myelinated fibers in the upper dorsal white communicant rami. As there are no white rami in the cervical region, all pain sensation referred over the cervical sympathetic trunk must descend to the upper dorsal region before it can reach the spinal cord.

Pain referred to the left, or right precordium and arm, enters the cord only on the same side.

The vagus nerve carries no important sensory fibers.

(2) Operation on the cervical sympa-

thetic trunk, even if it includes the stellate ganglion, cannot interrupt all the pathways of cardiac pain.

(3) The upper dorsal communicant rami or their sympathetic ganglia are the logical points at which to interrupt painful stimuli from the heart.

(4) These anatomical and physiological premises have been put to the test in 21 cases. In each instance where we have been sure of a successful block of the sympathetic rami in the segments of the referred pain, angina pectoris has disappeared.

(5) Alcohol injection is difficult technically, because of the depth of the rami and the small area sclerosed by the alcohol. However, it is the safest method we have and its results are distinctly better than in cervical sympathectomy. Forty-seven and four-tenths per cent of cases have been over 90 per cent improved, a further 26.3 per cent over 50 per cent, and only 15.8 per cent have been total failures.

(6) A patient with aneurysm of the ascending arch of his aorta was totally relieved of pain referred over the entire cervical and upper dorsal region on the right side by alcohol block of his first and second dorsal rami.

(7) In exceptional patients who are unusually favorable operative risks, we are beginning to remove the upper dorsal sympathetic ganglia, to avoid the 26.3 per cent chance of a poor result following an unsuccessful injection of alcohol.

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DISCUSSION OF PAPERS BY DRS. SWETLOW AND WHITE

Dr. Ernst P. Boas: I have had the opportunity of seeing quite a number of the cases which Dr. Swetlow injected, both before and after operation, and I can bear witness to the efficacy of the method in relieving very distressing pain.

I should like to confine myself, if I may, to a brief discussion of certain medical aspects of angina pectoris, and in particular to the indications for this form of treatment. The term angina pectoris is still used very loosely and many men are apt to consider heart pain and angina pectoris as synonymous. It is not mere academic quibbling to attempt to define this condition a little more exactly. After all, this method of therapy is not altogether innocuous and we should have our indications clearly in mind before we apply it.

From the clinical point of view we may roughly describe four major types of cardiac

pain. The first I should like to call heart pain and nothing else. It is a sharp sticking, stabbing pain, felt most often in the region of the apex, experienced chiefly by people with the so-called irritable heart or neurocirculatory asthenia without any basic organic heart disease. Similar pain is also experienced by patients with mitral stenosis. And finally, a soreness felt chiefly in the region of the apex is not uncommon in certain types of heart failure.

These forms of pain, which we need not discuss any further, are not at all related to angina pectoris; they are often quite unassociated with organic heart disease, and can usually be relieved by general medical measures. In these cases, in spite of the fact that the patients often show cutaneous zones of hyperesthesia, paravertebral injection is never indicated.

The next and most important group of cases are those with true angina pectoris. Their pain is determined by coronary artery disease; their symptoms were fully described by Heberden one hundred and thirty years ago. They experience pain under the sternum, but exhibit no change in pulse or respiration or blood pressure during an attack. The pain is usually induced by exertion or emotional stress, and is often accompanied or followed by zones of cutaneous hyperesthesia. These patients very often can be relieved of their pain by a proper medical regimen, and more particularly by a proper regulation of their life. If their activities are cut down, and they are given instructions which they will intelligently follow, with the aid of certain medication, probably the majority of them find relief.

In this group of patients paravertebral block should be used only when the pain is very frequent, very stubborn, and when all other methods have failed.

For the sake of completeness we should mention as the third group the severe retrosternal pain associated with coronary artery thrombosis, which differs somewhat from the pure angina of the previous group. In these patients, of course, paravertebral block is out of the question during the acute attack, which is usually associated with heart failure. Following the attack they are usually spontaneously relieved of their pain.

The fourth group of cases, possibly the most interesting, we may name "aortalgia," although that assumes a too definite knowledge of the etiology. It is a heart pain very much like that of true angina pectoris, felt over the upper sternum, induced very much as the pain of angina pectoris. These patients instead of being immobile with slow pulse and undisturbed respiration during the attack, are restless and nervous, are likely to toss in bed, or to walk about. There is a rise in heart rate and in blood pressure and a marked vasomotor reaction. The attacks occur particularly in nervous patients with hypertension, and in young people with rheumatic aortic insufficiency and in patients with syphilitic aortitis.

It has been my experience that these attacks are most difficult to relieve by medical means. A number of the cases that I have seen injected by Dr. Swetlow were of this group, and the method seemed to accomplish something here which could not be accomplished in any other way.

The introduction of the method of alcohol injection for paravertebral blocking has served two very useful functions: First of all, it has brought relief to a certain small group of patients who could get relief in no other way; and, secondly, it has acted as a counterfoil to the enthusiasm of the surgeons.

Dr. Swetlow indicated the many different types of operations that have been used by surgeons for the relief of angina pectoris. I agree in the opinion that all of these operations are unphysiological, that the mortality is very high, and that operation is never indicated. Formerly, before we knew of paravertebral block, in certain desperate cases where everything had been tried and had failed, we finally did resort to surgery because we did not know what else to do. Now we have a much better technic at our disposal, one which involves much less danger to the patients, and is much more certain of success. One reason why sympathectomy often produces such disastrous results is that with this method not only the afferent pathways through the sympathetic but the efferent, that is the accelerator fibers of the heart, are cut. Apparently the loss of this regulating function is not well tolerated by the heart. In the last issue of the *Archives des maladies du coeur*, Danielpolu has a very interesting series of articles, showing experimentally the damage to the dog's heart after the removal of the stellate ganglion.

Paravertebral block is a useful therapeutic measure, but one which should be restricted to cases of true angina pectoris or aortalgia.

It should be employed only in desperate cases, that is, in those with persistent pain in whom all other medical measures have failed.

Dr. Joseph Muir: The subjects treated in the papers to which we have just listened are of absorbing interest to me, although I have never taken any active part in either the surgical interruption of the paths of sensation responsible for the pains of angina pectoris or their elimination by means of toxic injections.

For several years past I have followed the work of Jonesco of Bucharest, and more recently of Lilienthal, the speakers of the evening and others whose work has been done in this country. When we consider that the pain of angina pectoris is probably the most exquisite and excruciating known to man, the sum total of relief from torture which these men have been able to afford suffering humanity, mounts very high.

The proposal and practice of alcoholic injection at once appealed to me as offering a means of escape from the dangers and discomforts which are the inevitable accompaniment of a surgical procedure of such magnitude as cervical sympathectomy, but when it later proved to be more or less temporary in its effects my enthusiasm underwent a certain modification. This same objection, of course, holds true of the methods of nerve blocking. As we have seen, any of these procedures can be repeated as occasion demands, but we are still without a permanent method of relief which does not involve the hazards of major surgery. That radium might possibly offer a way out of this dilemma had occurred to me not long after I decided to devote my attention exclusively to radium therapy.

The idea rested more or less dormant in my mind, however, until a personal accident brought the possibilities of radium in this connection very sharply to my attention. I developed a condition in the ethmoidal sinus for the relief of which a radium seed was inserted and permitted to remain permanently. Many months later I noticed a dimming of the sight of my right eye. Alarmed, I sought the advice of an ophthalmologist who, finding nothing, handed me over to an internist who, in turn, wished me upon a neurologist. While I was undergoing the various tests and explorations the light steadily faded before my right eye until it was totally extinguished.

Then at last we found out the cause. The action of the radium and the presence of the foreign body in the ethmoid, in close proximity to the optic nerve had destroyed its blood supply, so that atrophy of the nerve had taken place, that is, it had died of starvation.

Is it not reasonable to suppose that when we desire to eliminate nerves whose only function is to convey painful sensations, this same agent of destruction could be made to serve a most useful purpose?

The experiments of Mme. Dobrovolskia-Zavadskaia, carried out in the laboratories of the Paris Radium Institute, showed that when tubes of radium emanation were introduced into the muscular tissues of rabbits several concentric zones of tissue change were to be noted about the site of each radioactive center. In the middle was the zone of necrosis regularly noted whenever radium is inserted in tissue without filtration of the beta (caustic) radiation, or when secondary caustic rays are given off from metal filters. Beyond this zone of frank necrosis was another in which the muscle fibers remained alive, but because of prolonged gamma radiation, had undergone a noticeable diminution of their cytoplasm. This she termed the zone of atrophy, and it is evident that with proper filtration of both primary and secondary caustic radiation we may still be able to produce atrophy of muscular elements by sufficient exposure to gamma radiation.

The atrophy of the optic nerve in my own case was not due directly to the gamma radiation but to failure of the blood supply of the nerve. The changes induced in the walls of the blood vessels inhibited their function long enough to starve the nerve out. Subsequent regeneration of the vessels' musculature might take place, but the nerve would never be restored. So through my blind eye I now perceive a great usefulness for radium in the relief of angina pectoris.

Dr. Howard Lilienthal: I was much interested to hear the opinion of Dr. Boas on the value of surgery in angina pectoris and I was particularly pleased at his admission that he does employ surgery when he does not know what else to do; but no surgeon desires to operate if his patient can be cured by medical means. Whether the injection method or a cutting method is employed makes very little difference so far as this question of medicine and surgery goes, because both cutting and injection are surgical procedures. Doctor Swetlow's paper interested me much as a beautiful exposition of the pain conduction

paths and I willingly accept his demonstration as authentic.

It seems to me that we have to deal with 2 factors in the treatment of this distressing condition. First, the elimination of the disease which produces the phenomenon and second, the mere relief of the pain.

I regard the operations upon the sympathetic nervous system as directed against what I may call the spasticity of the cardiovascular system which is one factor, at least, of the disease itself. Relief of pain would be then incidental because the attacks would be replaced by a certain degree of permanent laxness of the vascular walls.

Second, the blocking of pain conduction which is what Dr. Swetlow's work so brilliantly accomplishes.

In purely spastic angina and especially in aortalgia, one would naturally give preference to the operation of cervical sympathectomy, or at least extirpation of the superior ganglion. When, however, there is actual damage to the heart or its vessels, it is difficult to see how an open operation could be of great permanent aid and I would give preference to alcoholic injection which I am convinced may make life again worth living.

The operation of sympathectomy has unfortunately not been taken up with the enthusiasm which I think it deserves. I believe that the cardiologists with their instruments of precision should be or will be able in many cases to determine which procedure is preferable in a given instance. The fact that the disease will not be permanently cured should not militate against sympathectomy. I have heard the objection raised that if the patient does not have pain he will neglect necessary precautions but I know that in some of my cases, unfortunately too few in number, the patient was able to feel when the attack was coming on by sensations though not of pain, and to behave accordingly, stopping his walk or other exercise and resting until he again felt normal.

In such a condition as angina pectoris which is not really a disease but a symptom, we are probably dealing with various pathological states and to argue for or against any one procedure is unscientific unless we know the cause and character of the disease which we hope to combat.

May I say I was very much pleased to hear Dr. White say what he did about the posterior mediastinotomy which is a favorite operation of mine in approaching these nerves. At the same time I do not see why this operation, although it is done under the eye and is perhaps, therefore, more scientific than the injection, should supersede the latter method. One should reach the spot accurately with the needle and there is little or no danger even if the pleura happens to be punctured. The needle may touch the bone, having traversed the pleura. Posterior mediastinotomy is a local anesthesia operation. I have done it many times for the exposure of the thoracic esophagus. The incision is the same as that for paravertebral thoracoplasty. Resecting the second, third and fourth ribs, you can get lots of room. The posterior part of the pleura is much looser in its connections with the bony structures than the part of the pleura further forward, and it is easily pushed aside.

Dr. Labat (Chairman): We have here 2 types of surgical procedures: (1) an operative *open* procedure, and (2) an operative *closed* procedure. The first open procedure is cervical sympathectomy. This has given, according to what came out this evening, less favorable results than the second open operation, which consists in the severing of the rami communicantes from the first thoracic to, at most, the sixth thoracic.

Inference may be drawn from what we have heard of the closed procedure that injections of alcohol may well replace the operations of sympathectomy and rami section, whether they be performed in the cervical region or in the dorsal region.

But the main point, and I think it is the most important factor, in this whole session was brought out by Dr. Boas who laid great stress on the necessity of differentiating between the pain, and said that alcohol injections should be reserved to those cases where a differential diagnosis pointed absolutely to angina pectoris or aortic pain.

This, I believe, should be our strict observance: the diagnosis should be well made in order that the treatment be well applied.

We are certainly very thankful to the speakers of the evening for the knowledge which they have brought to us of the pathways of pain in angina pectoris.

Dr. White (*closing*): I have very little more to add. The reason that we started operating instead of injecting the milder cases of angina pectoris was that in 2 of these we had had rather

poor results from unsuccessful alcohol injection. We then determined to make absolutely sure of interrupting the important nerve centers in the next suitable case.

I am sure that if you did this operation on the average old patient with myocarditis and severe angina pectoris, you would have a high mortality, probably as high as in the Jonesco operation. Therefore, it is an operation to be considered only in selected cases; in these I believe that it will avoid the 25 per cent chance of failure that we now have to face with alcohol. But I hope with improvement of the technic of alcohol injection that no operations at all will have to be used. These patients with alcohol injection have stayed in the hospital from three to five days, whereas a patient with any kind of operation is going to have to stay in for a week or two and he is going to suffer a great deal more than the patient treated with alcohol. That is a final point which is worth considering.

THE INTRAVENOUS USE OF THE BARBITURIC ACID HYPNOTICS IN SURGERY*

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WITHIN the last few years many new barbituric acid hypnotics have been synthesized and placed on the market. The individual recommendations of the manufacturers has raised the problem of the relative applicability and usefulness of each new preparation in modern medicine and surgery. The responsibility for this analysis must be equally shared by the clinician and the pharmacologist. The clinician has been, in many instances, compelled to rely on the verdict of the manufacturers relative to the characteristics of their product, with a consequent premature trial of a comparatively unknown drug. The pharmacologist, on the other hand, has found it practically impossible to keep pace with the manufacturing chemists in his scientific comparative evaluation, and has been able to give rather meager data upon which the practitioner can judge the relative usefulness and differential value of these drugs.

In order to alleviate this condition and as far as possible to answer questions about the barbiturates based upon experimental evidence as to characteristics, a comparative evaluation of the more common members of the series that are clinically employed was started in this laboratory over a year ago. It was hoped, in commencing this study, that if the results indicated actual differences other than their toxicities, it might be possible to evaluate these differences in terms of selective uses where the type of action desired could be brought about by a specific barbiturate. This result has been to some extent realized, and while the work is not completed to the end that the protocols are ready for publication, it is possible at this time to give a few indications of the trend of this research in terms of its clinical applicability.

In the first place, the hope that some of the newer barbiturates might give a deeper depression in like proportions of the fatal dose has not been realized in this laboratory. The toxicities of the various compounds have varied markedly, but the production of a comparative grade of surgical anesthesia in laboratory animals has required approximately the same proportion of the fatal dose in all cases. We are aware that some evidences have already been presented tending to show a difference in therapeutic efficiency, but these differences, in our experience at least, in so far as the depth of depression induced is concerned, have seemed to be less than the personal error in judging that depression. We do not mean to infer from this that there is no choice to be made and that one will serve as well as another in all instances. The selection of the proper barbiturate depends specifically on the type and duration of hypnosis that is desired. Small changes in structure result in marked variability in pharmacologic activity.

Before making any specific recommendation, we would like to analyze just what occurs on the intravenous administration of these drugs. The barbiturates are among the worst offenders with respect to the variability of dosage required to produce similar effects in different animals, or in the same animal at different times. There is no average "dose" of any of them that might not be dangerous to some individuals nor is there one that will produce sleep from the estimated dosage, in all cases. The attempt to estimate any

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fixed dosage is fraught with possibilities of considerable risk to the animal. These hypnotics must be given symptomatically, slowly, and with extreme caution, remembering that the maximal depression is reached probably fifteen minutes after the time of injection. Barbiturate deaths, particularly from long acting barbiturates, in just fatal doses, are almost never the immediate result of a maximal concentration of the drug in the laboratory animal. Pulmonary complications resulting from deficient respiration and loss of body temperature are usually the direct cause of death in experimental animals, particularly dogs. This is not so generally the case with the shorter acting barbiturates in which just fatal doses frequently cause death by respiratory depression. This situation should further emphasize the fact that the greatest danger to the patient may not be merely the depth of the immediate depression induced, but may result from complications developing hours later. The longer acting barbiturates are more liable to result in after-complications of this nature.

On the basis of our experience, we conclude that in no case should the attempt be made to carry the depth of depression to the stage of complete surgical anesthesia. In the first place, the amount required to produce complete analgesia is dangerously near the fatal dose. Laboratory animals are not always effectively anesthetized even when fatal doses are given. The barbiturates are not true analgesics and any attempt to employ them as such constitutes a usage that is bound to result in disappointment. Secondly, the anesthetist has no, or at most a variable and small, margin of safety upon which he can depend in case of unlooked for complications. When a drug of this type is injected intravenously, it is beyond reach so far as the anesthetist is concerned. He may hope that the patient has not received too much, but as far as an effective treatment is concerned, in case he has given too much. there is little he can do. Investigations at present under way in this laboratory give some promise of a possible antidote which may change this rather discouraging outlook.

A comparison that is not dependent upon the dubious differences in therapeutic efficiency, but upon the duration of marked depression, should be made. It would seem wise, unless some other condition made the contrary desirable, when giving a drug depressant that cannot be controlled after administration, to give a drug the effects of which in similar proportions of the fatal dose would pass off relatively quickly. This shortens the danger period in case of a slight overdose or difficulty of elimination, and lessens the possibility of pneumonic infection resulting from loss of temperature and respiratory depression and resulting weakened condition. This factor is of additional importance when one remembers other complications that occasionally develop from the use of an intravenously administered depressant. On recovery from any anesthetic, certain individuals tend to exhibit manifestations of excitement. This is probably dependent upon the fact that, in the partially recovered or half-conscious individual, the higher centers have not yet begun to function and he reacts as a medullary defensive animal. This fact is not altogether dependent upon postoperative pain stimulation. The same thing is frequently observed in unoperated animals in which pain could not possibly be a factor. The duration of this excitement period is dependent upon the length of time over which the depressant maintains the organism at that stage of consciousness. A gaseous anesthetic will display only transitory manifestations of excitement as it is rapidly eliminated. A long acting depressant, on the other hand, will maintain this condition at times for hours, depending on the length of time over which it acts. It has been this latter difficulty that has brought about some of the most serious objections to the use of the barbiturates in surgery. Occasional long periods of post-

operative excitement and mania are exceedingly undesirable. It is obvious that if this objection is overcome in a barbiturate, it must be accomplished through decreasing the length of time over which it acts. By making the period of action sufficiently short, it may be possible to simulate the fleeting excitement stage seen after use of a gaseous anesthetic.

There seem to be two possible approaches in developing a barbiturate of this type. Either the period of action can be shortened by using a barbiturate that can be more easily broken down by the body, or by the use of a more toxic barbiturate which will necessitate a smaller total quantity of drug to produce the desired effect. It is then necessary to destroy or eliminate a smaller quantity of drug before the body functions again become normal. Experience in this laboratory indicates that both possibilities may in part be realized.

The popularity of amytal has probably been largely due to the fact that it possessed over all the other barbiturates, the advantages which have been outlined here as being desirable. It is several times more toxic than barbital or luminal, and yet its advantages have been quickly recognized. Its shorter period of action has rendered it safer and the after-complications of excitement have been fewer. Its chief disadvantage seems to be that it is not short enough in its action for surgical purposes. It must be remembered that we are not speaking of the barbiturates in terms of their use by mouth as general hypnotics. The criteria of their value in that field may be entirely different from that of their use for the purpose of producing preoperative sleep. Long continued mild depression is certainly desired in many instances for which a longer acting barbiturate may possess a distinct advantage. This is not, however, generally true in surgical procedures where the welfare of the patient may be endangered by other factors than the depressant used, and for which purpose it is well to maintain a wide margin of safety. For such purposes, it is our opinion that a compound with a shorter period of action than that of amytal is of distinct advantage.

Our laboratory findings indicate that two different barbiturates furnish an approach to this type. These are secondary butyl-brom-allyl barbituric acid (pernocton) and ethyl-methyl-butyl barbituric acid. These two drugs are of approximately the same toxicity, with the latter being slightly more toxic. The duration of their action in experimental animals is shorter than with any other of eleven barbiturates we have studied. Postanesthetic excitation was observed in several animals, but was of considerably shorter duration with both drugs than with amytal or with barbital. The lowering of body temperature and slowing of the pulse and respiration were not marked, due to the shorter duration of action. These facts led us to believe that ethyl-methyl-butyl barbituric acid (Abbott) and secondary butyl-brom-allyl barbituric acid (Riedel-de Haen) would have greatest usefulness for intravenous use where the long action of other members of the series frequently resulted in disturbing complications.

Experimentally, ethyl-methyl-butyl barbituric acid is more toxic and has a shorter period of action than pernocton. This should result in a proportionate advantage when used clinically to produce preoperative sleep. These differences, however, are not so marked as those existing between amytal and pernocton; consequently, to demonstrate them in practice would require a large number of cases and careful checking of the postoperative period of depression.

After having established the foregoing criteria upon which the value of any barbiturate could be theoretically predicted, for intravenous usage, it was decided to make a comparison of the activity of these drugs in human cases.

The comparative toxicities were found to be the same as the laboratory results. To just produce sleep in a previously mor-

phinized individual required 0.6 gm. to 1.4 gm. of amytal, 0.4 gm. to 0.8 gm. of pernocton, and 0.2 gm. to 0.5 gm. of ethyl-methyl-butyl barbiturate. These were all injected as a 10 per cent solution with the exception of the latter which was occasionally given in a 5 per cent solution, the small volume of the 10 per cent solution that was required leading us to believe that a better control of the injection would result from the use of a larger volume of fluid.

We had felt that intravenous anesthesia produced by these drugs would be extremely useful in cases involving operative procedures about the upper air passages, and accordingly chose at first bronchoscopies and similar surgical cases. It was evident very early, however, that in doses that could be safely employed, the lack of depression of the pharyngeal reflexes, and the poor relaxation of the masseter muscles, made it inapplicable in this type of surgery. On the other hand, as a preparation for block anesthesia, and in particular for cases where extreme apprehension on the part of the patient added to the risk of the operative procedure, we have found the short acting barbiturates to be of advantage.

Attempts to use these drugs as a sole anesthetic agent even for minor surgical operations proved unsatisfactory. As was true with laboratory animals, the reaction to pain even with extreme doses was seldom completely abolished. It was necessary in practically all cases to supplement the barbiturate with a volatile anesthetic. A recognition of that fact indicates that they should never be used otherwise than as an adjunct to other forms of anesthesia; accordingly, the symptomatic administration should not be carried materially beyond the first indications of sleep.

The period of depression and sleep following the intravenous injection of these three barbiturates agreed with laboratory findings in so far as the contrast between amytal and the other two is concerned. Amytal produced, on the average, much longer sleeping time in proportional doses than did pernocton and ethyl-methyl-butyl barbiturate. The period of depression following pernocton as contrasted with ethyl-methyl-butyl barbiturate, however, did not parallel the differences that were demonstrated in the laboratory. The reasons for this are thought to lie in an insufficient number of cases as well as in the fact that it is more difficult to judge the cessation of a depressed state in the human than in the laboratory animal unless the differences between the drugs are quite marked. The experimental animal gets up on his feet as soon as the effects of the barbiturate have largely worn off, while the human may drift into natural sleep and rarely gives such easily recognizable indices of recovery.

Postoperative excitation and delirium have been occasionally observed with all three of the drugs. The duration of this period, however, was comparatively short with ethyl-methyl-butyl barbiturate and pernocton as contrasted with amytal, again confirming the laboratory findings. The long period of detoxification and depression with amytal and other long acting barbiturates constitutes a serious impairment of their value for surgical purposes. The short acting barbiturates mentioned here represent a distinct improvement and indicate possibilities and direction for further developments.

The availability of pernocton made up in a ten per cent solution is of advantage over the other two that are marketed in ampules of the crystals that must be made up into solution before use. It is possible that the other barbiturates will also be stable in this form.

There seems to be little advantage that can be claimed clinically for intravenous use of one barbiturate over another except in so far as the advantage lies in differences in the duration of depression and in the total quantity of the drug that the organism must destroy or eliminate. Then if the complication ensues that

the individual has a slow recovery as a result of faulty elimination or destruction, that difficulty will obviously be lessened by use of the more powerful and shorter acting drug. As adjuncts to surgical anesthesia, there has seemed to us to be a distinct disadvantage in long acting drugs, especially since the late effect is not one of pain relief, but of drowsiness and lack of cooperation, with the occasional complication of delirious reactions to sensory stimuli.

The immediate pharmacologic effects of the three drugs are apparently identical. A rapid injection results in marked respiratory and circulatory depression. When slowly injected a diminution of respiration is effected simulating that in normal sleep. Slight depression of systolic blood pressure is the rule. Some of the physical signs of depth of anesthesia ordinarily employed with drugs administered by inhalation are inapplicable. As an instance, we may state that the conjunctival and corneal reflexes disappear extremely early when barbiturates are employed. It is possible that a wider clinical experience with the barbituric acid derivatives may develop a group of distinct physical signs that will serve as a guide to their intravenous administration. At present a slow injection to the point of complete unconsciousness with moderate respiratory depression has been the extent of the guiding signs observed. The reaction to skin trauma may also be utilized.

Our present belief is that the barbituric acid derivatives administered intravenously promise to offer a worthwhile addition to the armamentarium of the physician. We doubt the advantage to the surgeon of the use of those derivatives which result in many hours or days of depression. We believe that the use of the quickly detoxified barbiturates may constitute in the future a very valuable background upon which to superimpose block or general anesthesia. A nervous type of individual can be taken to the operating room asleep. Whether this sleep be induced by the intravenous injection of a barbiturate or by the hypodermic injection of members of the opium and atropine groups, will doubtless be a matter that must be decided on the basis of long and careful clinical comparisons. None of the barbituric acid derivatives at present available appears to be a true anesthetic substance, and hence should not be considered for the replacement of the well established volatile and controllable anesthetic.

THE PLACE OF RADIOTHERAPY IN THE TREATMENT OF THYROTOXICOSIS*

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THE result of treatment of thyrotoxicosis can fairly well be measured by objective means accurate enough to compare the various methods of treatment in use. We can state with considerable accuracy the effectiveness of treatment in the individual patient, study a group of patients and state in definite percentage figures, the results obtained. We can do this in the case of thyrotoxicosis with greater accuracy than is true of many other serious diseases.

There are certain intangible factors in thyrotoxicosis that are not measurable. In a study of these patients we have no measure of temperamental changes; of feeling of well-being or the reverse; of psychic stability; except in a very crude sort of way, of general physical strength or capacity for work. These are the factors that the competent clinician "sizes up." But after all, these intangible factors follow a very close parallel with the tangible, measurable objective factors which he who runs may read. Of the tangible factors, the most important are the basal metabolic rate, the degree of return to normal body weight, the pulse rate and return to cardiac regularity where irregularity has existed. The clinical picture of thyrotoxicosis is so diversified that no one of these factors can be used as an absolute measure of the toxemia. Undoubtedly, accurate estimates of the basal metabolic rate constitute by far the best single means of estimating the patient's condition. For practical purposes it is a satisfactory guide in measuring up the condition of large numbers of patients. A combination of data on the objective factors mentioned here leaves nothing to be desired as a basis for study of results of treatment, and for comparison of the various kinds of treatment.

In presenting a study of some hundreds of clinical cases, it is impractical to present protocols such as constitute an essential part of the reports from experimental laboratories. But verifiable data should be given in detail, especially such verifiable figures as those of metabolism. The utter worthlessness of metabolism data when the source is not known and vouched for by the author, is notable.

In papers published by the writer, such data on metabolism were given. Since those papers were published some additional hundreds of metabolism estimates have been made upon these patients. All of these metabolisms were done under the conditions named in those papers, conditions which I regard as essential in any serious contribution to the subject; that is, they were done in my own laboratory, in expert hands, or in laboratories of such standing as to make their findings above question. No data obtained by mail, or from general practitioners, or from outlying hospitals are included. All patients whose metabolisms are done under such uncontrolled conditions are listed separately. They are excluded from the published cases as a matter of accuracy.

In answer to the question which constitutes the subject of this paper, some such data on the results of radiotherapy should be presented by those who favor this method of treatment. They are necessary for a critical study of any presentation. Yet roentgenological literature is peculiarly lacking in this respect. No paper gives diagnostic data; few give sub-

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stantial objective data on which the critical student may base an opinion of results. In many roentgenological contributions, it is apparent from the context that the metabolism data given are quite uncontrolled, or it is stated that the observations were made by the physicians sending the patients for treatment.

Among the more valuable contributions to radiotherapeutic literature, the incidence of cure is rated from 50 to 80 per cent. A frequently recurring error in stating results is to list patients as "improved." Pathologically and prognostically, a patient whose metabolism has dropped from 60 to 30 as the result of any kind of therapy is no more improved than is one whose metabolism has risen from 0 to 30. In either case, such a patient is in urgent need of proper care. On that basis, all improved cases must be listed as failures.

Another factor that is given all too little prominence in roentgenological literature is the time element required for the cure of the patient. In many cases the time factor plays an important part in the organic damage sustained by the patient. It is apparent that much time is required for *x*-ray treatment, during all of which the patient is in a toxic state. Exception is taken to this statement in an exceptionally valuable contribution by Christie who states that the average time required is five months, and that he has seen no damage develop under treatment. Yet in the same paper he states that much of the "morbidity" and "ravages" of the disease are due to the fact that the duration of the disease averaged "over two years" before the patient came for treatment. Five months is a substantial fraction of two years; if the treatment averaged five months, many of the patients must have remained toxic while under treatment a much longer period; and finally, from the context of his earlier papers, a substantial proportion of his patients remained under treatment more than seventeen months, and were toxic and under treatment at the end of that time.

Radiotherapy has had much advocacy as a preparatory method for bad risk patients. It has seemed to me that iodine given for ten to thirty days has been far superior in its effects and surely much more rapid in action. Patients who have been given iodine over long periods of time seem to become resistant to its action. These may very logically be given the benefit of radiotherapy preparatory for operation.

Very mildly toxic cases, and particularly early adolescent cases often respond readily to iodine, rest, etc. without obtaining complete relief. Radiotherapy may have a place here in making such improvement complete and lasting.

It has been repeatedly suggested that the inoperable cases are best treated by radiotherapy.

What is "an inoperable case?" An accompanying inoperable carcinoma, the existence of any accompanying condition such as advanced tuberculosis, that reduce life expectancy to a minimum. These may properly be considered inoperable. No degree of thyrotoxicosis is in itself a bar to operation. No associated condition, cardiac central nervous, etc., that is not intrinsically incompatible with life, constitutes a contraindication to surgery. If, with the removal of the burden of thyrotoxicosis, life may be expected to be reasonably prolonged, there is no contraindication. These patients may be controlled more effectively within a few weeks with iodine than by prolonged *x*-ray therapy. Those who have associated conditions incompatible with life may be made more comfortable with iodine, to which *x*-ray treatment may bring additional aid.

The mortality of thyroidectomy has been reduced to a remarkable low figure. It is below 1 per cent among surgeons competent in thyroid surgery. Its results begin to be apparent within twenty-four hours of the operation. The metabolism approaches the normal within ten days.

Data on the permanence of results are all too few to satisfy the critical student.

Some such figures are about to be published by the writer. The following statement may be made in this preliminary paper.

Among 1000 thyrotoxic patients subjected to thyroidectomy, on whom we have adequately studied and recorded data, obtained under the restrictions mentioned here, *not one* whose metabolism reached normal after operation, and remained normal over more than a single observation, has had a relapse.

Of the small number of patients operated upon by the writer who required reoperation because of a relapse, about 15 patients, *not one* had had a normal metabolism after operation, except possibly for a single observation. Though clinically cured, actual metabolism studies showed that they were cases of technical failure due to an inadequate thyroidectomy. In each case the secondary operation revealed an excess of thyroid tissue overlooked or the amount left underestimated at the primary operation. These were not relapses, but errors of operative technic.

Of over 50 patients operated upon elsewhere, who came under observation for what was supposed to be a relapse, many with a history of clinical cure before the relapse occurred, very few had had their clinical condition checked up with metabolism studies. Of this few, *not one* had had a normal metabolism for more than a single observation. Yet this type of patient is often regarded as evidence of the failure of surgery instead of the failure of the particular surgeon concerned. Under these circumstances, adequate thyroidectomy must be granted to insure an almost perfect freedom from relapse.

The utterly uncritical spirit in which these failures are regarded in radiological literature is most unfortunate. Thus an outstanding roentgenologist refers to a patient whose metabolism fell from +115 to +112 after operation as having had a "subtotal" thyroidectomy! Of course the veriest tyro in physiology would have known the type of surgery to which that patient must have been subjected. The further statement that many of his patients had a higher metabolism after thyroidectomy than before does not justify serious discussion.

SUMMARY

Radiological literature relating to the treatment of thyrotoxicosis is extremely meager in adequately controlled objective data on which the student may base an opinion. Even on the basis of this inadequate study, from 20 to 50 per cent of failures are commonly admitted.

Very mild, early, adolescent cases and patients with associated lesions incompatible with a reasonable life expectancy, may advantageously be given radiotherapy.

Radiotherapy offers no advantage over a short course of iodine as a preparatory method of treatment.

NON-SURGICAL TREATMENT OF HYPERTHYROIDISM*

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CHICAGO

THE treatment of the syndrome usually called exophthalmic goiter or hyperthyroidism has gone through a number of changes since the initial efforts, especially of Kocher. His results, due to a removal of too much thyroid and parathyroid, caused a loss of enthusiasm in the surgical treatment which has, however, reappeared in recent years especially since the successes of such men as Crile and the Mayos. The question of treatment and end-results revolves very largely upon the criteria that are used in evaluating the amount of the patient's involvement. The almost universal use of the basal metabolic test has resulted in its being considered as the principal criterion as to cure. Other factors are the reduction in pulse rate, and one that is quite generally overlooked, gain in weight. These are selected because other evidences of cure are of such an individual nature that it is very hard to compare statistics with a rigid differentiation as to the amount of involvement.

Nevertheless, in the actual dealing with the patient there are many symptoms of which he complains that are not indicated by any one or all of these criteria. Many patients will show normal metabolism, normal pulse rate and moderate to excessive gain in weight, and still be far from well. It has seemed for a long time that this warrants the idea which has been set forth by Warthin and others, that we are not dealing with a disease that is restricted to the thyroid, but rather a constitutional disease, and that by the removal of the thyroid or its over-activity, whether by surgery, *x*-ray, the injection of boiling water or other destructive substances, or even by rest, we produce a remission of the disease very similar to the remission produced in pernicious anemia by liver therapy. As in pernicious anemia with liver therapy, the achylia and nerve symptoms may continue in the presence of perfectly normal blood picture, so in thyroid, although laboratory tests may be perfectly normal, we still have a group of much more indefinite symptoms that often continue. These are best illustrated by the following case history.

CASE 1. Mrs. H., aged thirty-five, had been under observation for a number of years because of an old rheumatic mitral disease. She returned with an obviously marked exophthalmic goiter. The onset was insidious during the past three months, with a loss of 15 lb. in weight, increasing weakness, nervousness and fatigue. There were the usual toxic symptoms of free sweating and a number of attacks of diarrhea. Basal metabolism at this time was +75. Against my advice she elected operation and this was done by a well-known thyroid surgeon who did what is termed a subtotal thyroidectomy, without the removal of the parathyroid tissue. Within ten days basal metabolism was reported to be +1. She was kept under observation by the surgeon for a period of three months, during which time she gained in weight, had a normal pulse rate and continued with normal metabolism. When seen at this time she complained of an indefinite train of symptoms best expressed by her as "not feeling her normal self." These consisted of easy fatigue, lack of energy and sleeplessness. She volunteered the statement that she had felt much better at the height of her toxemia than she now felt. Careful examination revealed muscle irritability, a positive Chvostek and muscle cramp. Blood calcium determination gave 10 mg. per 100 c.c. of blood. The administration of 60 grains of calcium lactate in milk, with an equal amount of lactose per day, produced slight changes in the tetany. Because of the well-known physiological fact that thyroid increases calcium metabolism, she was given 2 grains of thyroid daily. This resulted in increase of blood calcium to 12 mg. per 100 c.c.

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and complete disappearance of the signs of tetany. The administration of thyroid made no change in metabolism. The other symptoms showed very slight improvement and it was not until after eighteen months of this treatment that she felt able to return to her duties as a bookkeeper. She has never had a return to a sense of complete well-being.

It has been noticed many times in individuals with very great reduction of the thyroid rate, that the giving of a sufficient amount of thyroid to bring metabolism to normal often results in complaint by the patient that they do not feel as well under medication as without it. Going on the assumption that these patients find it impossible to readjust their sense of life suddenly from low metabolism to normal or slightly above normal rate, we have found treatment much more satisfactory when thyroid therapy is very gradually increased, so that instead of reaching normal basal metabolism within a short time, a period of a year or more is allowed elapse. It would appear logical that the same thing may occur in individuals who have been used for varying periods of time to very marked increase in the metabolic rate, namely, that a sudden reduction of this rate to normal or less than normal requires a varying period, often a long one, for a readjustment of the individual to bodily sensations that occur with a normal rate.

The principal claim of surgery to treatment of hyperthyroidism is, first, its immediate and permanent eradication of the toxemia, with a practically negative mortality rate in the hands of skilled operators. This prompt cure would appear to be extremely important to individuals whose economic status is such that they are unable to stand a prolonged illness. But if it takes a year or more for these patients to return to a normal sense of well-being, it may then be seriously questioned whether surgery does so promptly eradicate the disease.

A second argument in favor of immediate removal of the thyroid is that a continuance of toxic thyroid symptoms means an increased serious damage to the heart muscle, so that non-operative treatment may cause a symptomatic recovery with a very serious cardiac lesion left as a residue. Observation of a number of cases with severe cardiovascular involvement treated by *x*-ray has convinced me that the prolongation of treatment by *x*-ray does not increase cardiac damage, and that the ultimate recovery of cardiovascular symptoms is just as good under this form of therapy as any other.

Although in the hands of an expert operator the mortality from surgery is extremely low, the probabilities are that the mortality statistics from the country as a whole, in the hands of all operators, would be considerably higher. If this be true, then a third reason for the use of conservative means against surgery is that of reduction of mortality.

The remission is produced by destruction of the gland, regardless of the manner in which it is destroyed, and often a remission may be produced without active interference with the gland. Neisser, Ewy, Spengler, in European clinics, Solomon Straus in America, have suggested in certain types of moderately toxic thyroid, the use of bed rest, with very small doses of iodine 2 to 2.5 mg. daily. These authorities have all reported favorable results under this method of treatment.

This treatment is especially applicable in girls and women, and occasionally in men in whom a prolonged illness is not a serious economic factor. If a carefully selected group such as this is kept under observation for a year or more, by far the greater number may avoid any destructive type of therapy.

In our own experience we have a series of 42, mainly young girls and young pregnant women, with basal metabolic rates as high as +35, who on small doses of Lugol's solution, 5 to 6 drops a day over long periods of time, have shown complete remission of their toxic symptoms with no return for periods varying from one

to two years. In more toxic types and in those in whom small doses of Lugol's solution fail to produce recovery, the gland may be destroyed with a varying degree of rapidity by the use of irradiations with *x*-ray. E. L. Jenkinson, of Chicago, in a personal communication, recently stated that in 600 cases treated only by *x*-ray, 80 per cent have remained free from abnormal basal metabolism or pulse rate. He believes that very often only a small part of the thyroid is involved in a pathological process, and that the destruction of this particular part results in a cure, regardless of the remainder of the thyroid.

Groover, Christie[1] and their co-workers report a series of 305 cases treated exclusively by *x*-ray. Their criteria for recovery is that of gain in weight and lowering of basal metabolic rate. In this group 37 were mild, 157 were moderate, and 111 were severe; after treatment, 271 were considered as cured, 88.85 per cent; 26 were improved, 8.52 per cent; and 8, or 2.63 per cent, were unimproved. In this group there was not a single case of injury to the parathyroid, although this has rarely occurred as a consequence of large doses of radiation, in the hands of others.

In a small series of personal cases we have had only one that has not given satisfactory results with radiation (Case 11).

Case 11. A woman of fifty gave a history that could be explained as a chronic hyperthyroidism with periods of remission and exacerbation, extending over some twenty years. When first seen in January, 1928, she was suffering the most severe exacerbation she had experienced. There was a loss of 10 lb. in weight, a chronic diarrhea of two months' duration, extreme nervousness and sleeplessness. Her thyroid was moderately enlarged and distinctly nodular. A moderate exophthalmus was present, and also a fine tremor of the hands and tongue. The apex of the heart was in the anterior axillary line. At rest the heart rate ranged around 120 per minute. Basal metabolic rate at this time was 38.6. She was given a series of *x*-ray treatments as shown in the following table:

[1] Groover, T. A., Christie, A. C., Merritt, E. A., Cox, F. O., McPeak, E. M., Roentgen irradiation in the treatment of hyperthyroidism. *J. A. M. A.*, 92: 1730, 1929.

Table 1

Date	Area	Filter, Mm.	Voltage, Kv.	Skin Focal Distance, Cm.	Milli-amperes	Time, Minutes	B.M.R.
2–29–28	Ant. thymic	6 Al.	125	12	5	12	47.8
3– 1–28	Right thyroid	6 Al.	125	12	5	12	
3– 1–28	Left thyroid	6 Al.	125	12	5	12	
3–21–28	Ant. thyroid	4 Al.	105	12	5	7	43.6
3–23–28	Ant. thyroid	4 Al.	105	12	5	7	
5– 2–28	Ant. thymic	1 Al.	75	15	5	5	27.2
5– 3–28	Right thyroid	1 Al.	75	15	5	5	
5– 3–28	Left thyroid	1 Al.	75	15	5	5	
10–17–28	Ant. thymic	1 Al.	75	15	5	6	38.6
10–18–28	Right thyroid	1 Al.	75	15	5	6	
10–19–28	Left thyroid	1 Al.	75	15	5	5	
11–19–28	Ant. thyroid	4 Al.	105	15	5	7	37
11–22–28	Ant. thyroid	4 Al.	105	15	5	7	
12–20–28	Ant. thymic	¼ Cu. 1 Al.	125	15	5	15	32.8
12–21–28	Right thyroid	¼ Cu. 1 Al.	125	15	5	12	
12–21–28	Left thyroid	¼ Cu. 1 Al.	125	15	5	13	
1–11–29	Ant. thymic	6 Al.	125	12	5	10	29.7
1–22–29	Right thyroid	6 Al.	125	12	5	8	
1–23–29	Left thyroid	6 Al.	125	12	5	8	

After her return from her summer vacation, September 29, her basal metabolism was normal, and she had gained 15 lb. in weight. Her heart was still dilated, and there was some dyspnea upon exertion. When she was seen within the past week, the cardiac symptoms had disappeared and she considers herself as completely well.

As to the differentiation of hyperthyroidism into the adenomatous type or the exophthalmic type, many authorities do not feel that an accurate diagnosis can be made. Christie has concluded that the results of *x*-ray therapy are the same in both types, and my personal experiences agree with these conclusions. Besides active treatment, the patient should be kept as near bed rest as possible, if at all toxic.

The average duration of treatment is approximately four months in the more toxic type of cases. It is preferable that the first series be given with the patient in the hospital at bed rest. It has been our custom to prepare them for *x*-ray therapy with large doses of Lugol's solution, as for surgical operation. With reduction of the symptoms therapeutic *x*-ray is given over a period of two or three days, depending on the toxemia of the patient. If there is no reaction and the patient is not extremely ill, he is allowed to be ambulatory until the next series of irradiations. Usually after the second series he can be treated as an outpatient, and many can return to work. All moderate and mildly toxic cases are treated as ambulatory cases, and among the men practically all continue at their work.

Case III. Mr. L. consulted me on May 11, 1929 because of nervousness, fatigue, weakness and rapid loss of weight. He showed the clasical symptoms of an exophthalmic goiter. These symptoms had been noticed during the past month. His first basal metabolic rate was 38.7, pulse 110.

His business is of such a nature that his entire year's income is derived from three months' work during the summer. During this period he travels considerably and regularly works eighteen hours a day. The occurrence of symptoms at this time made any treatment other than ambulatory impossible. He was hospitalized one week, given Lugol's solution, 45m per day, and received his first *x*-ray treatment May 31, 1929:

Table II

Date	Area	Filter, Mm.	Voltage, Kv.	Skin Focal Distance, Cm.	Milli-amperes	Time, Minutes	B.M.R.
5–31–29	Right thyroid	5 Al.	118	23	5	5	38.7
5–31–29	Left thyroid	5 Al.	118	23	5	5	
6–1 –29	Ant. thymic	5 Al.	118	25	5	5	
6–27–29	Right thyroid	5 Al.	125	30	5	7	
6–27–29	Left thyroid	5 Al.	125	30	5	7	
6–28–29	Ant. thymic	5 Al.	120	30	5	7	

It became more convenient for him to continue his treatments nearer his office, accordingly the following 4 series were given in a downtown office:

He continued to work at high tension during this entire period. After July 1, 1929, the nervousness, weakness and rapid pulse were greatly improved, but no gain of weight occurred until he was able to stop his work in September. A recent report was that of normal weight and apparent complete recovery. His basal metabolic rate is now +5.

It is unquestionable that there is a distinct place for both surgery and medical treatment of hyperthyroidism, with the majority of patients probably being better off on medical therapy than on surgical therapy, but I feel quite sure that in the

future our ideas of so-called hyperthyroidism will have changed so completely that all our present theories as to therapy will be discarded.

TABLE III

Date	Area	Filter, Mm.	Voltage, Kv.	Skin Focal Distance, Cm.	Milli-amperes	Time, Minutes	B.M.R.
8- 9-29	Right thyroid	4 Al.	120	11	5	6	
8- 9-29	Left thyroid	4 Al.	120	11	5	6	
8-12-29	Right thymus	4 Al.	120	11	5	6	
8-12-29	Left thymus	4 Al.	120	11	5	6	
8-16-29	Posterior neck	4 Al.	120	11	5	6	
8-30-29	Right thyroid	4 Al.	120	11	5	6	
8-30-29	Left thyroid	4 Al.	120	11	5	6	
9- 1-29	Right thymus	4 Al.	120	11	5	6	
9- 1-29	Left thymus	4 Al.	120	11	5	6	
9- 5-29	Posterior neck	4 Al.	120	11	5	6	
9-23-29	Right thyroid	4 Al.	120	11	5	6	
9-23-29	Left thyroid	4 Al.	120	11	5	6	
9-27-29	Left thymus	4 Al.	120	11	5	6	
9-27-29	Right thymus	4 Al.	120	11	5	6	
9-30-29	Posterior neck	4 Al.	120	11	5	6	
10-14-29	Right thyroid	4 Al.	120	11	5	6	
10-14-29	Left thyroid	4 Al.	120	11	5	6	
10-16-29	Left thymus	4 Al.	120	11	5	6	
10-16-29	Right thymus	4 Al.	120	11	5	6	
10-18-29	Posterior neck	4 Al.	120	11	5	6	

RADIOTHERAPY

ITS PLACE IN THE TREATMENT OF TOXIC THYROID DISEASE*

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WHAT is the best treatment for exophthalmic or toxic goiter? This question is asked frequently by patients who suffer from this condition. Judging from the voluminous surgical literature on the subject, the casual reader feels that surgery is the answer. However, radiologists who have given the question much thought and who have reviewed their own results, feel that radiotherapy must be given thoughtful consideration. Inasmuch as toxic goiter is a disease of questionable origin, we must agree that there is no specific treatment. Surgery cures by excising a major portion of the hyperactive gland, while irradiation by *x*-ray or radium produces a similar effect by decreasing secretory activity of the individual cell in the gland. Neither method has shown itself successful in all cases, but surgery has made patients well who have shown little or no response to radiotherapy, while irradiation has cleared up cases that were still toxic after one or more surgical attempts.

The earliest use of the *x*-ray in exophthalmic goiter is recorded by Williams and Pusey, two outstanding American physicians, who reported marked improvement following its use in this condition. At about the same time, two German investigators, Stegman and Goel, noted the lasting effects observed after the roentgen ray was administered to patients with this disease, and Charles Mayo, who speaks today with authority on surgical treatment, reported that *x*-ray therapy was valuable in preparing toxic patients for operation. In 1905, Abbé, a New York surgeon, began to use radium with success in patients of this type. Since those days, many other men throughout the world have reported their experiences. The outstanding articles have been written by Allison, Erskine, Dunham, Forssell, Hayes, Henry, Holmes, Holzknecht, Jenkinson, Loucks, Pfahler, Soiland, Swanberg and Trostler. A careful review of their writings will convince the most skeptical that in radium and *x*-ray we have weapons which, if not considered as rivals, at least are valuable adjuvants to surgery in toxic thyroid disease.

Not all patients who present themselves are suitable for radiotherapy. There must be a careful selection to eliminate those with simple colloid goiter and those with adenomata. These patients complain of enlargements and pressure symptoms, and can only be relieved by surgical intervention, since irradiation will produce little if any diminution in the size of the gland. However, if a patient is suffering from a toxic adenoma and has refused operation, or if operation is contraindicated, there is no objection to treatment, as there is a good assurance of diminishing the toxicity even though there is no change in the size of the palpable lobes.

To insure a proper conception of suitability and cooperation on the part of the patient, the following points should be stressed:

1. Careful history and examination to know that a toxic goiter is the basis of symptoms.

2. Verification of the degree of toxicity by basal metabolic readings.

3. Eradication of foci of infection which may be the underlying predisposing cause of the toxicity.

4. Institution of irradiation with the following reservations and explanations to the patient:

(a) Irradiation causes a diminution of

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toxicity but it can in no way remedy existing vascular or neurologic defects already present.

(b) Irradiation effects are slow in their manifestation, so that patients must cooperate and be under observation for at least a year.

(c) Institution of rest and quiet in advanced cases, and the administration of such suitable medication as is indicated for complications and sequelae that may already exist.

(d) Metabolic readings during the course of treatment to prevent over-irradiation.

If these suggestions are observed and followed, there will be little chance for failure.

Every kind of treatment has its drawbacks. Irradiation of the thyroid has run the gamut of objections, but the principal one is the occurrence of so-called burns. It is true that a radiodermatitis is seen after treatment occasionally, and in the days when radiotherapy was in its infancy, when little or nothing was known about filters, this was a legitimate objection, but under present conditions, such an occurrence is a rarity. Accidental omission of filters may be followed by dermatitis, but has its counterpart in the accidental cutting of a recurrent laryngeal nerve during thyroidectomy.

Another argument against radiotherapy is the danger of myxedema. This is a real danger, and it must be admitted that intensive prolonged irradiation results in hypothyroidism. However, removal of too much thyroid tissue will do the same thing. If frequent metabolic readings are made during the course of treatment, the occurrence of myxedema will be infrequent. When the rate drops to plus 15 per cent, no more exposures should be given until a period of six or eight weeks have passed to note whether the rate is dropping further or is rising again.

The last objection raised is the increased difficulty of operation when irradiation fails. Prolonged irradiation, especially with soft rays, may result in fibrosis, but the fibrosis resulting is no different from that caused by applications of iodine and hot water injections. Although the oozing may be increased, the surgical risk is less, since it is admitted that irradiation reduces the degree of toxicity. Careful selection of patients, and the abandonment of prolonged radiotherapy where symptoms are not improved, will eliminate this phase.

If these, then, are the objections, what are the advantages of radiotherapy? In the first place, the treatment per se carries no mortality. We agree that in the hands of the expert surgeon this is very low, but in the hands of the occasional surgeon it is still high enough to warrant consideration of other types of treatment. Our modern existence is governed by economic conditions. In recommending one or another form of therapy in toxic goiter, this must be borne in mind. In other words, how long will it take until the wage earner is back at work and how much will his regular routine of life be disturbed? Much of the irradiation is given to patients who are ambulant; that is, they are home patients rather than hospital patients, and they continue their work if they are not too toxic. Judged from this standpoint, a patient treated by irradiation suffers less disturbance of home life, with less expense, than one submitting to the surgery. However, this should not necessarily be an argument for radiotherapy, for if financially able it is just as advisable for a real toxic patient who is receiving radiation therapy to spend a short time in the hospital as it is for one who is being prepared for operation. Thus, the number treated by radiotherapy who need hospital care is materially less than those submitting to surgery.

In the early part of this paper we mentioned that no treatment is 100 per cent successful. Radiotherapy has its failures, and the concensus of opinion is that these are due to:

(a) Lack of cooperation on the part of patients. They tire of waiting for results and submit to other forms of therapy.

(b) Improper diagnosis.
(c) Lack of radiosensitivity.

The latter patients belong to a class indistinguishable from others with general toxic symptoms and increased metabolic rates, who show no response to radiation. There has been much speculation as to the cause of this failure of response. Radiologists who are using harder forms of *x*-ray generated from 180 kv., filtered through copper, feel that a change in technic from moderate voltages of 135 and 140 kv. to 180 or 200 kv. will eliminate some of these failures. Likewise, radium enthusiasts seem to have more success than those using the *x*-ray. Possibly a change in technic as is being used in the treatment of malignancy, with harder rays, prolonged exposures and higher filtration, will give the desired effects.

To get at the actual results, we have studied a series of over 3100 cases treated by radiotherapy, reported by twenty different observers. This study gave the following results: Seventy-three per cent were clinically well, they showed no evidence of thyroid disease clinically or metabolically; 16 per cent were improved; 11 per cent were unimproved and must be considered radiological failures. Included in these 3100 cases were 400 patients treated with radium by one observer alone. Ninety-eight per cent were clinically well following the use of gamma radiation, which seems to verify the comments made in the paragraph preceding that a recourse to harder radiation will attain more perfect results.

In view of the foregoing presentation, we feel that the results of radiotherapy in exophthalmic or toxic goiter compare favorably with those obtained by surgery. Happily, patients who do not get relief from one method of treatment are benefited by the other. For this reason, we are of the opinion that it is justifiable to advise the use of irradiation in toxic thyroid disease, and if failure results, operation can still be carried out since the surgical risk is not increased.

CHOLECYSTITIS

WITH AND WITHOUT CHOLELITHIASIS*

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IN the course of the lifetime of the busy physician and surgeon, certain phases of his chosen profession seem to receive much more thought and attention than others. Since the day of specialization is at hand, it is but fitting that we at this time show some specific study and thought along lines that are of special interest to us. It is because of this interest and study that I have chosen to present one of the common causes of digestive symptoms, a complex of symptoms exceedingly numerous. I refer to diseases of the gall bladder and ducts. The frequency with which this organ is affected cannot be ascertained since it is estimated that most of the human race at some period of their life, suffer from some one of the many pathological conditions of this organ. Neither males nor females seem to be immune, although it is found in women more often.

It is because of the many cases of so-called dyspepsia and indigestion which have proved to be caused by pathological conditions of other organs, that I present a few cases of cholelithiasis. Space will permit but a cursory introduction to this subject concerning which volumes have been written. That stones should develop at all in the human anatomy seems a phenomenon almost unbelievable. Seeing, however, is believing and we have all seen them many times. I will simply mention a few of the causes which are necessary for the formation of gallstones.

Cholelithiasis is a most common disease, much more common than was formerly supposed. Many cases of so-called gastralgia, acute and chronic indigestion, ulcer of the stomach, diseases of the pancreas and appendicitis prove to be gallstones. Osler states that gallstones are found at autopsies in from 5 to 10 per cent of all cases that die of other causes. If this be true, what a common malady it is! It is true that other diseases affecting the pylorus, the duodenum, or the head of the pancreas are sometimes diagnosed as gallstones. Unless there are very positive signs of cholelithiasis it is often very difficult to make a positive diagnosis. The *x*-ray and fluoroscope are at times valuable aids in diagnosis. There are cases of gallstones that give absolutely no symptoms of the disease. A stone or stones may remain quiescent in the gall bladder for a long time. This is shown to be true by the fact that they are found at operations and autopsies.

The formation of these stones is an interesting process concerning which much has been written and a great many theories expounded. The accepted view today is that there are two primary factors which must be present: (1) some interference which causes either a stasis or impediment to the free flow of bile; (2) some kind of bacterial infection. It is necessary that both these conditions be present; the one without the other is not sufficient. It is generally a mild catarrhal inflammation which distorts and either closes or partially closes the cystic or hepatic or common ducts and thus produces the first necessary cause, namely, some interference with the free flow of bile. The reason that gallstones do not form when there is a free flow of bile is that there is no stagnation of bile and the inroad of infection is cut off by the flow of bile washing bacteria back into the intestine. The second cause, that of infection, is produced by many kinds of bacteria, some of the most common being the Bacillus coli communis, the Bacillus typhosus, Staphylococci pyogenes aureus and albus. Cases are also recorded

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where the infection was produced by the pneumococcus and by the bacillus of influenza. There are many avenues by way of which these germs are carried to the gall bladder. They may enter from the duodenum through the common duct or the portal circulation, and the hepatic artery may carry them to the gall bladder, or they may enter from the peritoneum through the walls of the gall bladder itself. It is seldom that infection takes place from the duodenum because, if the duodenum is in a normal condition it is supposed to be sterile. Any disease of the duodenum favors infection of the gall bladder by extension of the trouble through the common duct. One of the most common ways for infection to be carried is by the portal vein and the most common organism found is the colon bacillus. The Bacillus typhosus may enter through the circulation from the blood or direct from the intestinal tract.

Cholelithiasis is a subject which is of vital importance and interest to both physicians and surgeons. It is of interest to the internist from the diagnostic point of view. I believe the condition a surgical one and that treatment should be surgical. It is not rare to find in cases of gallstones, with chronic cholecystitis, that ulceration of the wall of the gall bladder takes place to such a degree that the gall bladder may rupture, throwing the stone or stones into the peritoneal cavity, or that cholecystoduodenostomy and cholecystogastrostomy have been performed by nature.

The size and the number of the stones vary greatly. Merkel found one that weighed 120 gm. As many as 7802 stones have been found in a single case reported by Otto.

I will not enter into the discussion of the predisposing causes or of the medical treatment, if there be such a treatment.

Case 1. This case is a most extraordinary one from a surgical point of view. Mrs. S. aged forty-nine, born and reared in England until she was twenty-three years old. Father died at the age of forty-two with pneumonia, the mother at the age of fifty-three of heart disease. There are four brothers and three sisters all living and well at the present time. Patient married at the age of twenty-two, has three children. Lived in Canada three years and six months, when she moved to Syracuse and has lived here ever since.

About two years after coming to Syracuse she had her first sickness. Was taken with what was then called inflammation of the bowels, probably appendicitis with perforation of the appendix, producing a general peritonitis; was critically ill for ten weeks when she began to improve and was finally able to be up and about but never fully recovered. Following this sickness she consulted another doctor who, after examining her, told her she had a tumor of the womb and advised operation for its removal. She was removed to the hospital and the tumor removed. Made a good recovery. About six months after she began to be troubled with obstinate constipation, often going for a week at a time without evacuation. It was in such a condition as this that she was taken violently ill with intense pain in the abdomen. All the ordinary methods of producing catharsis were resorted to, but to no avail. It was impossible to get any response from the bowels. Finally it was decided to remove her to the Hospital of the Good Shepherd, where she was operated on for intestinal obstruction and a portion of the intestine removed. From this operation she made a good recovery. About four weeks after leaving the hospital she took a severe cold. During a coughing paroxysm she felt something give way in her groin and she began to have great pain; was again removed to the hospital and operated for femoral hernia. Two years after she developed a lipoma on her left shoulder. It grew very rapidly in size, so large that it interfered with the movements of her arm, so she decided to have it removed, which was done.

December 16, 1904, I was called to see her. She had fallen the day before and injured her left wrist. Upon examination I found she had a Colles's fracture which was reduced by the usual methods.

March, 1904, she again consulted me concerning a pain in the stomach. She said pain would come on most any time independently of whether she had eaten or not. Said she had had this pain off and on ever since she had inflammation of the bowels some twenty

years before. At first the pain was mild in character and did not cause her much inconvenience. The pain had gradually increased in severity until now sometimes it seemed as if she would die. Pain was right in the stomach. The attacks would sometimes hold off for several months and then she would have another spell. It would begin with loss of appetite, even the smell of cooking food would nauseate her; then she would begin to vomit and would be deadly sick, cold perspiration standing out on her forehead. She would be very dizzy. The pain in her stomach would be paroxysmal in character and so severe that she would have to get on her hands and knees. The character of the vomitus would be stringy mucus mixed with bile. Vomiting would not in any way relieve the pain. External applications and also medication, even morphia administered hypodermically, would not relieve her. On physical examination heart and lungs were found to be normal. Abdomen revealed scars of former operations, aside from which I could detect nothing abnormal. Liver was slightly enlarged. I could not palpate the gall bladder, neither could I outline it by means of percussion. Urine: sp. gr. 1025, acid, no albumin, no sugar. Bowels irregular.

Diagnosis: Catarrhal gastritis, suspicious of gallstones. I restricted her diet as to quantity and allowed only foods that could easily be digested. I also told her that she should not work so hard. She was doing all kinds of work, from washing clothes to pitching hay; in fact, I think she could tire out almost any man. Medical treatment was directed towards aiding digestion. She seemed to improve under this line of treatment. I treated her in this way for about a year.

September 3, 1906, I was hurriedly summoned. Upon by arrival at the house I found the patient suffering agonizing pain. She could not keep still; would pace up and down the room, wringing her hands, at times even falling to the floor in her intense suffering. My first thought was to relieve her as quickly as possible so I injected ¼ grain of morphia immediately, then gave her a few whiffs of chloroform. In about one half hour she began to be somewhat relieved so that it was possible to make a physical examination. I found the abdominal wall tense and board-like. The right rectus muscle was especially noticeable, standing out above all the other muscles. There was pain and tenderness over the whole right side of the abdomen. There were no points where the pain was more severe than in other points. The whole right side of the abdomen seemed involved. The tongue was coated, there was nausea and vomiting. She was unable to retain anything in her stomach. The vomiting was persistent, lasting three days, during which time the pain was incessant, at times more severe than at others. The temperature ranged from 101°F. to 103°F., pulse from 110 to 120, respirations, 26. At no time was there any jaundice, neither had she ever had any jaundice. The condition, as before stated, lasted for about one week. September 9, or about one week after the onset of the sickness she was removed to the House of the Good Shepherd. The day after her condition began to improve. A positive diagnosis was not made but gallstones was the prevailing opinion.

The following day a cholecystectomy was performed by me. The gall bladder showed thickening from the frequent exacerbations of cholecystitis. The gall bladder was completely filled with three large stones and six small ones and pus. The cystic duct was entirely occluded. Gall bladder was so full of stones and pus that when incised the pus flew out in a stream of some distance, so great was the pressure within. Had this case not been relieved by operative interference the gall bladder would have burst, throwing the gallstones and pus into the abdominal cavity with probably fatal results. The patient made a speedy recovery and today is in good health.

As we look over the foregoing history there are several points which impress themselves upon us: first of all, the length of time this patient had gallstones. The thickness of the gall bladder and the size of the stones suggest this. In my opinion the trouble in this case started when she was a young women suffering from frequent attacks of gastritis which became chronic, the condition extending into the duodenum and thence into the common and cystic ducts of the gall bladder. If this be true we have one of the necessary causes of stone formation, the swelling and thickening of the mucous membranes producing an impediment to the free flow of bile. The other necessary cause, that of infection, arose when this case had inflammation

of the bowels, which was probably caused by the ruptured appendix producing general peritonitis. This patient had many other severe illnesses, and yet no one ever discovered the gallstones or the cholecystitis. The treatment had been for the catarrhal stomach condition.

Again we find this disease in a woman who worked for a living and at hard manual labor. We are told in textbooks that this condition is rare in an active person, in fact, sedentary habits are a predisposing cause of the disease.

Case II. Mrs. C. of Buffalo, has always been in good health except for frequent bilious attacks. Sometimes would go months without any digestive symptoms or bilious attacks. These attacks she attributed to nervous exhaustion. Is never affected unless she has attended some particular meeting or convention in which she has had an important part, either in discussion or paper reading. It was while attending a convention in this city that this patient came under my care and attention. These so-called bilious attacks would generally follow mental excitement and worry. They would begin in the epigastrium, this discomfort increasing until she would become extremely nauseated and finally vomit. Several years ago vomiting would relieve her and if proper care was taken of her food she would steadily improve and convalescence would be short. She has thus suffered this kind of attack for many years.

She had a rather strenuous week in Syracuse attending a convention and had retired for the night when she felt pain in the stomach and was nauseated; consequently she drank some hot water and some soda and began to vomit. She vomited at intervals all night and the following day without relief. She was removed to the Homeopathic Hospital for careful observation, the vomiting continuing. There was general abdominal pain and tenderness. The abdominal wall was now becoming tense. Pain and tenderness marked over the appendix and gall bladder. Blood count showed leukocytes, 12,000. I advised operation which was refused. Doctor J. W. Candee was called in consultation. He also advised operation and immediately. After much discussion the patient agreed to be operated.

Consequently, at 8 P.M. I removed an acutely inflamed appendix. Believing the frequent attacks of indigestion and also the bilious attacks to be due to the trouble in the gall bladder, the right rectus incision was carried up so as to expose the gall bladder. Bringing the gall bladder up into the incision, it appeared somewhat increased in size and very hard, the gall bladder was filled with stones and the internal pressure greatly increased. A trocar and cannula were introduced and about 6 in. of thick bile removed. An incision was now made into the gall bladder and 5 large stones about the size of hickory nuts were removed. In the cystic duct were 3 smaller stones. These were removed through the gall bladder. Rubber tube drainage was introduced in the usual manner and the incision closed. Recovery was uneventful except that she developed phlebitis of both legs.

Case III. Patient thirty-three years of age. Family history negative. Two brothers and two sisters living and well. Married and no children, and no female trouble to her knowledge. Menses regular and normal. Has complained for the last five years of attacks of indigestion so-called. Would be taken with pain in the pit of epigastrium and would vomit. Vomiting would relieve her, but now she says the more she vomits the more she feels like vomiting. The nausea is continuous. Pain is also constant, not free from pain at any time in these attacks. Had been under the care of many doctors and had a great deal of treatment for digestive disturbances. She would finally improve and recover. It was during such a sick spell as this that I was called in consultation. Physical examination revealed an abdomen hard and tense, with general abdominal pain and tenderness, temperature 101°F., pulse 110, blood count showed marked leukocytosis. I advised removal to hospital and operation. Diagnosis, acute cholecystitis and possible gallstones. She was removed to the Homeopathic Hospital and the high incision parallel to costal cartilages of the right side made, the gall bladder exposed and opened. It was filled with very thick bile mixed with pus. The cystic duct was entirely occluded by a single stone. This I removed through the gall bladder and the usual large size rubber tube drainage was used.

I have briefly reported these cases of cholelithiasis to show how frequently these

common cases of so-called dyspepsia and indigestion prove to be gallstones.

I believe in routine examinations of the gall bladder. In cases requiring the opening of the abdomen, when there is no contraindication, the gall bladder should always be examined to discover the presence of stones, to ascertain whether or not it is collapsible, to discover adhesions aptly called by Morris "cobwebs in the attic of the abdomen,"[1] to see whether the wall of the gall bladder is thickened from attacks of cholecystitis and to search for any other pathological conditions around the gall bladder which influence it from without.

Who opens the abdomen today who does not examine and remove the appendix? Pathological or normal, the appendix is removed unless there is some reason for not doing so.

I am just as firm a believer in examinations and treatment of the pathological conditions of the gall bladder. Should any be found I think the time to treat these cases is at the first sitting, so-called, that is, providing there is no contraindication. In this way many second operations could be avoided. In many cases of cholelithiasis the symptoms are not in the gall bladder. You do not have to suffer from an attack of biliary colic to have gallstones. Colic formerly was supposed to be produced by the passage of the stone. Of course this might cause severe pain varying with size of the stone and condition of the ducts. Seldom have stones been found in the feces following an attack of biliary colic. We believe the intense pain and agony to be produced by the violent peristalsis. The gall bladder and ducts, endeavoring to rid themselves of the stones or viscid bile, contract so violently that colic is produced, called biliary colic.

This idea is further substantiated by the fact that gallstones are found in feces where there has been no colic or pain, proving that their passage has been painless. In the great majority of cases of gallstone disease you have, at some particular time and generally at irregular intervals, attacks of intense, agonizing, unendurable pain commonly called gallstone colic. The picture of a patient afflicted with gallstone colic is common to us all and a further description will not be given. It is these attacks of excruciating agony that bring these cases as a rule to the surgeon.

Concerning the treatment of these cases, when the stones are confined to the gall bladder, there is a difference of opinion, some favoring cholecystectomy; others claim cholecystotomy and drainage to give the best result.

My method has been to perform cholecystectomy unless there is some contraindication, such as in the very old, and feeble, or where for anatomical reasons the removal of the gall bladder would be fatal. I have chosen these cases to show the different clinical pictures presented.

In the first case we have a patient that was unfortunate enough to have had her abdomen opened on more than one occasion and with a gall bladder full of gallstones causing digestive trouble continually and yet undiscovered and unrelieved; a typical picture of gallstone disease with the colic, vomiting, shock, etc. I know that many times while operating, conditions arise which make it impossible to do all that the surgeon thinks necessary. In such cases it is excusable to wait until some further time. I think it is the duty of the surgeon to tell the patient of the existing pathology and recommend further operation. I believe it the duty of the surgeon to make a thorough examination of the abdominal contents. Because you have discovered abnormalities in one part, is no reason to believe that others in the same subject do not exist. It is for this reason that a thorough intra-abdominal examination should be made to discover pathological conditions or beginning pathological conditions that exist, causing trouble and discomfort without having been diagnosed previous to celiotomy.

Since we have decided that this is a surgical disease, the operation to be used is also of initial importance.

DIAGNOSIS AND TREATMENT OF GALL BLADDER DISEASE*

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SINCE Graham's epoch-making method of diagnosis (1924) by the intravenous injection or the imbibition of sodium tetraiodophenolphthalein little of importance of a similar nature has been brought to the notice of the profession. Various liver functional tests have been proposed and while they are not exactly of diagnostic importance, they do give us an index of the work the liver is capable of performing. Indirectly, they sometimes help in making a diagnosis, but they are especially directed to guide us in the selection of the case for a proper operative procedure.

I believe the dye test is being used universally with varying results in helping us to measure the function of the gall bladder. Before the use of this test a positive diagnosis of cholelithiasis by the use of the *x*-ray was about 15 per cent. Graham and his associates believe that 98 per cent of diseased gall bladders can be correctly diagnosticated. This percentage is probably a little high, but there is no question that with the introduction of the Graham test we have been better able to arrive at more logical conclusions in reference to the diseased gall bladder. Erroneous ideas concerning the function and the physical characteristics of the gall bladder occur very often as a result of the conclusions reached after reading the *x*-ray plate. Here, as always, we depend on the personal equation of the man reading the plate. A gall bladder which, for instance, empties itself well after the ingestion of the fat meal, does not necessarily mean a healthy gall bladder, while on the other hand, one that does not empty itself well is surely the seat of some pathological condition. This has often been substantiated at operation. Only rarely does it follow that a gall bladder that does not empty itself after the fat meal, is found at operation to be normal. Certainly all these cases must have had symptoms, otherwise the test would not have been made. The dye test often misses stones, but it may be said in support of the test that it usually finds them. Only recently 2 cases have come under my observation where the single stone type was missed. In the one, a pure white cholesterol stone was found at operation. It was the prettiest gallstone I have ever seen and no amount of *x*-ray would have revealed it. In the other case, there was no excuse for not revealing the presence of the stone. Last week I operated on a case which, according to the results obtained from the dye test, should have shown very decidedly a diseased gall bladder. The test showed that the dye did enter the gall bladder well, that after the fat meal the dye was not expelled normally. We found a gall bladder, not particularly diseased, its luster somewhat dimmed, and there were no stones. We removed the gall bladder and found the cystic duct patulous.

Diagnostically, bile drainages have assumed for me an entirely new place in the separation of those cases possessing gallstones and that large class of cases that have symptoms without gallstones.

I always believed in bile drainage from the standpoint solely of helping to make a diagnosis, and have so stated on many occasions. Its curative properties always were doubted and I still adhere to that belief. Some patients are temporarily relieved of symptoms, while I have found a few who were made worse by the drainages, which at times brought on an acute attack of colic.

It is easier to diagnose cholelithiasis after a drainage than after an *x*-ray; it takes less trouble and it is certainly less expensive. It may be a startling statement to make when I tell you that I would rather depend on the microscopic diagnosis

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than upon the *x*-ray diagnosis. The former is especially helpful in those cases where the radiologist has reported no stones in the presence of all the classical symptoms. Several cases have come to operation where the radiologist has reported no stones, when the miscroscope revealed the presence of crystals and pigment. Their presence I consider a pathognomonic laboratory sign of cholelithiasis. While it is always better to make a diagnosis of stones on the presence of crystals alone or pigment alone, preferably the latter, one or the other has been sufficient on which to make a diagnosis. The infallibility of this laboratory test is so well known in the services of the hospitals with which I am connected, that it becomes an easy method for the interne to perform and does not require any expensive equipment. Still, I do not think it will displace the *x*-ray. Firstly, because patients demand this method of examination and secondly, in order to keep hospital records up-to-date, we usually request the *x*-ray examination. Also it makes the two examinations a fine means of comparison and a good check up, one against the other.

The Van den Bergh test is a fine method for the separation of the obstructive types of jaundice from those of the non-obstructive.

The icterus index test, while not nearly as useful as the former test, still is of interest in showing the diurnal variations of the depth of jaundice in obstruction.

It has always been foreign to my method of presenting a paper to begin the discussion with laboratory methods, since invariably I consider the history of the case of prime importance. Laboratory methods can never supplant or supersede the history that one receives from the patient. This caution must always be sounded because there is still too much dependence being placed on laboratory methods before a good history has been obtained.

One can never forget the symptoms of a patient in the midst of an attack of acute gallstone colic. The patient suffers excruciating pain of varying degrees referred to the right upper quadrant. The pain may extend to the shoulders, right or left, usually the right. There may be severe headache, the pain radiating there instead of to the shoulders. Almost always the pain comes on at night, but it may appear at any time of the day. If the patient suffers a gallstone attack at night, characteristically the patient will be free of pain by daylight. Certainly there are many modifications of these phenomena. The patient vomits a little bile, or there may be several paroxysms lasting hours. Coupled with these symptoms a physical examination will almost always make the correct diagnosis. In gall bladder disease, tenderness and rigidity are always present in the right upper quadrant. If nephrolithiasis is present, there will be tenderness and rigidity in the lumbar region, or a little higher in the loin space. Attention to this palpatory diagnostic sign will be of great help in separating gallstone colic from that of the colic due to stone in the kidney.

It is not so easy, however, to separate the signs of an acutely inflamed high appendix from that of gallstone colic. These appendices are usually undergoing gangrene, but if perforation ensues, the pain disappears, followed by localized and later, general peritonitis.

While an acute pancreatitis may sometimes be difficult to separate from acute gall bladder colic, there ought to be very little trouble in the separation of these two. There is no affection so painful as that of acute pancreatitis. The mere fact that morphine has little or no affect ought at once to put us on our guard. General peritonitis and a board-like rigidity accompany the pain, which are the two signs that one must always remember.

A mild, fleeting attack of pancreatitis is difficult to differentiate from gallstone colic. The symptoms are the same with the possible exception that in pancreatitis there may be a slight conjunctival jaundice. Here also the microscopic drainage test is of great value in separating the two affections. At operation the diagnosis is rather easy because the pancreas is harder than normal. The hardness may not per-

vade the whole pancreas, but may affect the head, the tail, or part of its body. The appropriate treatment here is one of the drainage operations, either internal or external, preferably the former. It is rarely difficult to separate a perforated ulcer from an attack of acute gallstone colic.

General peritonitis with its board-like rigidity is never found in patients suffering from acute cholelithiasis. Hence, it is most important that we be on our guard in the separation of the symptoms of this quadrate of infections, namely, cholelithiasis, acute pancreatitis, acute perforating ulcer and acute appendicitis.

Occasionally, attacks of angina pectoris are confused with gallstone colic, but there is usually very little difficulty in distinguishing these two conditions. There is, however, a slow toxic effect on the heart as a result of a long continued infection of the gall bladder. It may present itself in the form of an extra systole or a myocardial change which may even make the operation a hazardous one. There is no question that some of the unaccountable deaths which follow a cholecystectomy may be traced to a damaged heart as a result of a chronically inflamed gall bladder. We have done a lot of work along these lines and have invariably found that the heart has been much benefited after operation. There is always a temporary remission and in some a permanent good effect.

It is impossible to go over the whole category of gall bladder infections, but I would like to refer to that most interesting symptom, jaundice. Jaundice, as a symptom, is probably the most important single sign that one can encounter in the whole realm of gall bladder disease. It may be of two kinds, obstructive or non-obstructive, known as the hemolytic type. The latter is an interesting condition and must be separated from jaundice due to stone, tumor or adhesions. The latter are especially difficult to separate when accompanied by painless jaundice without a blood picture. Painless jaundice is always found in the hemolytic type. This form may also be present in gall bladder disease and its passage-ways, in which case we must be suspicious of some malignant condition. In hemolytic jaundice a physical examination will present an enlarged spleen, because this organ is unable to destroy the red blood corpuscles quickly enough, while in gall bladder disease the spleen is normal in size. Hemolytic jaundice is curable by means of a splenectomy and the results are most gratifying.

Obstructive jaundice gives one an entirely different condition to cure. Its causes are many, the most common being a stone in the common duct. Other causes are tumors of the pancreas, of the papilla of Vater, adhesions within or without the common duct, stones in the hepatic ducts or the small ducts of the liver, diseases of the liver and the various types of liver conditions causing pressure on the parenchyma and its bile capillaries. The surgeon and some internists and gastroenterologists are still at variance as to the proper time to operate on these cases. Some as yet believe that there is still the so-called catarrhal jaundice. This, I believe to be a fallacy, because in my opinion there is always some obstructive influence to account for the jaundice. A case in point is one on which I operated upon just a few days ago. This patient was a young man, aged thirty. He noticed about ten weeks ago that he was jaundiced; there were no other symptoms present, no pain, no discomfort or even digestive disturbances. We kept him in the hospital three weeks before we suggested operation. Drainages did no good, therapeutically speaking. At times a light-colored bile was obtained, but duodenal contents were mainly aspirated. No B bile was ever obtained. At operation we found a stone in the gall bladder, and in addition, a swollen head of the pancreas causing obstruction to the flow of bile through the papilla of Vater. The gall bladder was not removed, but drained as it is a rather hazardous thing to do to remove a gall bladder in the presence of jaundice. The common duct was explored and found to be free of stones. It also was drained.

It would not be profitable to discuss

with you the category of operations for the relief and cure of cases having obstruction of the common duct. At times the general practitioner asks the impossible to relieve patients of their jaundice. This was recently illustrated in two patients who had only slight jaundice following a cholecystectomy. There were symptoms of partial obstruction about every two weeks, but these were always relieved; in the one, by means of drainage with the Rehfuss tube, in the other, by the opening of an external sinus. I advised against operation in both of these cases, because they were leading a life of comparative comfort. After having visited other consulting surgeons, they were advised to undergo operation. I operated on one of these cases, the other operation being performed by the consulting surgeon. Both women were on the table for three hours. In my case the common duct was found after two hours of searching with a hypodermic needle; in the other case the common duct was not found at all. However, there are cases in which obstruction is complete, when there is no other alternative but to operate and relieve it by means of an internal or external drainage operation. I am referring now to those cases that have previously been operated upon and some disturbance follows in the common duct causing complete obstruction. One must never underestimate the dangers involved in operating on these cases, because great difficulty is encountered in finding the common duct, especially when the obstruction is due to adhesions, or injury of the common duct at or near the hepatic ducts. The longer the time consumed in the operation the greater is the danger to life.

Just one more illustration of the stamina with which patients can withstand three major operations in the space of a few weeks is worthy of record here.* A man fifty-two years old was sent to the Mt. Sinai Hospital with symptoms of gall bladder disease. He had been studied by eminent physicians and there was some difference of opinion among them concerning his condition. The gall bladder was removed without difficulty; in fact all marvelled at the ease with which it was removed. On the third day the patient developed jaundice; this became worse as time progressed and after four weeks from the time of the first operation we opened him again; the common duct could not be found after we had searched for an hour. We closed the wound with the knowledge that he would not be benefited by this operation, but with the firm conviction that he would be operated on again after he had recovered his balance. As predicted the jaundice did not improve; in fact he was developing symptoms that portended disaster. The abdomen was opened again three weeks after the second operation and the common duct was found in twenty minutes from the time the abdomen was opened. A tube was placed in the hepatic duct, the distal end was placed in the stomach and then the stomach was sewn down close to the duct. The jaundice disappeared rapidly. He is now making a nice recovery.

*This patient was operated upon for the fourth time by the Walton technic for reconstruction of the common duct. Bilirubin has reappeared in the stools.

SUMMARY

1. The Graham test is of considerable value in helping us to diagnose diseases of the gall bladder.

2. The microscopic examination of bile obtained by the Rehfuss tube in the duodenum is of great value in detecting the presence of stones in the gall bladder. It has given 100 per cent positive results.

3. No tests, however, can supercede the taking of a careful history of the patient.

4. We must always be on the alert to differentiate gallstone colic from other acute affections of the abdomen.

5. Jaundice may be obstructive or non-obstructive, painful or painless.

6. When absolute obstruction is present, an operation must always be performed. In partial obstruction the greatest judgment must be used in operating.

CONSIDERATION OF THE METATARSALS AND THEIR INJURY*

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AN expression for consideration of fractures of the metatarsal bones is presented, with the hope that something upon the subject, in a broader sense than that which is ordinarily given, will be of interest to the surgeon, whose province is in the field of bone and joint surgery.

The gross anatomy of the metatarsals is such that we may describe these bones as a group in regard to shape and position, with relation and function much in common. All articulate proximally and distally with bones for support and joint service. Interosseous muscles and ligaments bind them snugly together into a bundle and assist toward maintaining this relation more intimately with the distal tarsals, (from within outward, the internal, the middle and the external cuneiform and the cuboid bones). Proximally the metatarsals participate only in a gliding motion upon these tarsals and their adjacent metatarsals. These bones are of the long variety, presenting a rather long and slender shaft with large proximal and small distal ends or heads. The respective shafts of all these bones are slightly bowed, the upper surface being rounded and the entire shaft arched slightly with the convexity directed upward. They taper generously from the tarsal end forward to the phalangeal end, while the narrowed surface of each metatarsal is directed downward to the plantar surface of the foot. The tarsometatarsal heads are rather flat while the metatarso-phalangeal heads are almost hemispherical. Distally the metatarsals ride freely so that the head functions as a base in the metatarso-phalangeal articulation. The uncommon anatomical features of the metatarsals are not of sufficient significance to warrant particular concern for fracture treatment.

Mechanical Consideration of the Metatarsal Bones. This group of bones spreads out distally from the tarsometatarsal articulations to enter in the formation of the five digits of the foot. The metatarso-phalangeal joint or the distal metatarsal articulation accomplishes all of the movements of each digit, viz.: adduction, abduction, flexion and extension. The metatarsal bones enter collectively in the entire formation of the transverse arch and in the partial formation of the longitudinal arch. It is the damage to these bones, their ligamentous or muscular attachments which, if not properly considered, lowers, relaxes or destroys either or both of these arches.

Combined Foot Movements as Related to the Metatarsal Bones. At this point the combined foot action, inversion and eversion must be mentioned. These come about mostly with the action of the astragalo-calcaneal joint, but the ligamentous attachments to the joints anterior to it assist in completing these movements. No movement of the foot need be stressed as of value unless applied with the function of support and progression. The longitudinal and transverse arches are very important in the performance of these acts.

Progressions. There are several performances of foot function during walking. The movement in the first act, is raising the foot from the surface. In the second act the body-weight is rocked anterior upon the lateral and medial piers of the longitudinal arch. In the third act the weight should be relieved from the outer or lateral pier and transferred entirely to the medial pier or pod. The fourth act is accomplished as the body load is further thrown to the ball of the great toe or the distal end of the first metatarsal bone, the

* Submitted for publication February 26, 1930.

distal end of the medial pod of the longitudinal arch, which pushes the body forward as the opposite foot passes through a similar series of movements, beginning as its mate leaves the surface.

Susceptibility to Injury and Permanent Impairment. The metatarsal bones with their attachments are an intricate, closely related and firmly built-in bony group with muscles and many ligaments for support and movement. It is, therefore, not astonishing that these parts are frequently and readily injured. They are quite susceptible to damage which is ordinarily overlooked after the subsidence of the acute symptoms immediately following injury to the foot. Fracture-tears or fracture sprains are a common type of trauma to the foot architecture and their seriousness is not sufficiently evaluated. Possibly, more fractures go unattended in this particular location than in any other portion of the skeletal structure unless it might be the digits. Furthermore, even recognized injuries to the bones of the foot occasion a surprising lack of concern. Many patients of this sort allow a painful foot to go unattended for weeks or months. Of course, in such instances, it is not uncommon to find a fallen arch (splay-foot) or even more serious and possibly irreparable damage. Relaxation of the ligamentous structures is likely to occur with unattended fractures in this location and reconditioning of these parts consequently goes beyond the simpler methods for correction. An unreduced metatarsal fracture occasions distress and serious deformity to the foot and is more to be dreaded than a poor or vicious union.

Causes of Fracture of the Metatarsal Bones. Fracture of a metatarsal bone occurs either from direct or indirect violence. Probably the most susceptible and most frequent metatarsal to fracture is the fifth. It is the one which is commonly subject to individual fracture by indirect violence, such as sudden twisting or turning on the outer pier of the longitudinal arch. Direct violence, as a crush, from a weighty object passing over the foot, or a blow from a heavy falling object, is the commonest factor for metatarsal fracture.

Types and locations of fractures of the metatarsal group are numerous. They may be such that one or several of these bones enter the injury. The fracture may be with or without displacement, and as either it may be simple or compound. We may have a fracture-tear, a complete or incomplete fracture, or any of the great variety of fractures to which long bones are subject. When the fracture is one without displacement, little concern about trauma to the soft parts is necessary. When, however, there is displacement, there are possibilities of complications, such as joint injury, rupture of blood vessels, nerve injury and severe destruction to the musculature. When a metatarsal fracture is not of the compound variety there is little danger from any of these complications, even though there should be considerable displacement of the fragments. In the case of a compound metatarsal fracture the most serious issue to combat is infection.

Subjective Symptoms. The history of some distinct foot injury will commonly be given. After such injury the foot becomes very painful and there is swelling with difficulty or inability to use same. The pain generally radiates upward into the musculature of the lower leg, peroneal muscle region, and forward to the one or several toes associated with the fractured metatarsal. In less severe cases there may be only rapid swelling and discoloration. There is aggravation of pain on motion, as during efforts to function.

Objective Symptoms. In the more severe cases the subjective symptoms are masked, more particularly since the patient is in a state of shock of variable severity. Great pain is elicited, when the patient's general condition is unaffected, during efforts at motion or manipulation at and about the immediate location of fracture. There is distinct point-tenderness over the fracture site. Impact by forcing the toe of a sus-

pected metatarsal toward the tarsal group elicites sharp pain. Crepitus may or may not be present. There may or may not be mobility of fragments. In preference to eliciting such symptoms, and when little doubt remains in the mind of the surgeon that there is severe injury, it would be more advisable to rely upon the evident symptoms. The *x*-ray should always be depended upon. It will locate, detail and confirm any fracture of the metatarsals without causing discomfort.

Diagnosis. Metatarsal fractures might be confused with fracture of adjacent bones, contusion or sprain. The *x*-ray will remove doubt about which of these conditions should be eliminated, although it is very common to find such fractures complicated with any or all of these. The allied injuries with which fracture of the metatarsal bones might become confused require the same treatment at the outset, namely, rest. In such an event the injury under observation is diagnosed by exclusion, with the further findings of symptoms, and as a last resort, with the findings of the *x*-ray.

Treatment of Simple Fractures. The sooner proper immobilization of a metatarsal fracture is instituted the better will be the end-result. Where there is no displacement it is often advisable to allow no disturbance of fragments by manipulation, because with proper splinting the part will correct itself. Little or no deformity should result in such cases so long as there is some end-to-end thrust of fragments, with full consideration being given to the factor of neutral muscle-pull. Neutral muscle-pull materially assists in bringing into normal relation properly supported bony fragments. Where there is marked displacement it is advisable to increase the deformity and then to endeavor reduction. Ordinarily, the fracture of one metatarsal produces little or no displacement and the part may be immediately placed in a plaster-of-Paris cast.

Treatment of Compound Fractures. Most of these fractures are of the comminuted and displaced variety. They are considered as infected wounds. Frequently, because of the gravity of infection or because of irreparable maceration of the soft parts and the fear of gangrene, amputation is considered early. This should not, however, be too hastily undertaken. Give the damaged tissues every encouragement for regeneration and assist them with proper antiseptic measures to overcome infection. The constitutional evidences of the patient can at all times be the guiding factor for decisions relating to removal of fragments which, it is hoped, may be spared for possible restoration to function. Doctor Fred Albee says, about any severe trauma which threatens sacrifice, "Save every fraction of an inch." It is not a bad end-result which establishes ankylosis because of infection. A deformed foot can still prove very functional and reconstructive work can always be considered with spared structures. It is better to chance the battle with a compound fracture of the metatarsals than to sacrifice promiscuously, as an early drastic procedure, crushed components of the foot. The common but not a real interference with conservatism for fullest restoration to function is time. A deformed metatarsal is better than one which is removed. In severe compound injuries always endeavor to save the traumatized structures, establish splintage of the fractured metatarsals early and remove all displaced fragments which are unattached. Convert all compound fractures to simple fractures as speedily as possible. The commonest and most serious problem to overcome in the effort will be infection and the dangers therefrom are minimized with modern antisepsis. After a compound fracture wound has been rendered clean, no matter how complicated the fracture may be, such injury merits the ordinary treatment for simple fracture, viz.: reduction of fracture, proper immobilization and aseptic surgical dressings for the open but sterile wound. Do not endeavor the reduction of a compound fracture until complications

of infection are safely overcome. Traumatization of the soft parts during efforts at reduction is not unsafe in a surgically clean area and need not imply reinfection.

Reduction and Immobilization. In treating all compound fractures the feature of changing dressings until the open wound is closed, should be primary. When this is accomplished the fracture becomes one of the simple variety and reduction, at even so late a time as four weeks after the accident, may be safely undertaken by the closed method. When the bony fragments of a metatarsal fracture are well approximated it is ready for immobilization, preferably in a plaster cast. Such a cast should extend from the base of the toes to about 3 in. above the maleeoli. This large type of cast is advised in fracture of any of the bones of the foot, individually or collectively, barring phalanges. No dressing will accomplish the ideal immobilization of a plaster-of-Paris cast, and although splintage with some other form of support may be obtained this dressing, after closure of any wounds and final reduction of the fracture, is best. All patients should be advised to go about early upon crutches with no weight-bearing upon the injured foot. Thus, on the first day after reduction the patient is to be encouraged to go about when there are no contraindications. No metatarsal fracture should be immobilized in a cast for less than three weeks. Where the factor of compounding complicates matters the treatment of this factor becomes a separate consideration and subsequent immobilization in the cast should not be for less than three weeks beyond the period of closure of the wound. For a week after the removal of the cast the foot should be kept from supporting full body-weight. Massage with active and passive movements of the entire foot and ankle may be instituted for ten-minute periods several times on the first day following the removal of cast. Hot bathing or baking is very beneficial and during such, active movements of toes and ankle are of value. Active movement periods in time lengths should increase with each day and fuller weight-bearing with less support from the crutches should be correspondingly encouraged. On account of the importance of the metatarsals in weight-bearing, it is ill-advised to use the foot for full body-support in less than one week after removal of cast. When several metatarsals are involved or when the tarsals enter the injury it would be well to increase the period for restoration to full function from four to five weeks. After a four-week period of complete immobilization in this type of fracture weight-bearing may be gradually increased from day to day taking more and more of the load from the crutches and placing it cautiously and gradually upon the injured extremity.

Osteogenetic formation in fracture begins most actively about four days after the injury. Calcification of the area for union is the last and slowest process in the formation of the callus. When a callused area does not calcify sufficiently the soft bony growth under strain gives to such a degree as to cause a relaxation or stretching of the ligamentous attachments. This danger must be fully appreciated before permitting the use of a foot with a freshly reduced metatarsal fracture. Complications to be expected from too early use of foot for weight-bearing, are disturbing and harmful, the impairments resulting therefrom, contributing to dysfunction.

Case Reports. The following cases are illustrations of some of the varieties of metatarsal fracture treated:

Case 1. Mr. C. H. S., aged forty-seven, moving-man. Severe injury to the first metatarsal bone of the left foot, caused by a heavy piece of furniture falling across same. Became weak and sick for a short spell. After recovery continued to walk upon foot during day of accident. Pain and swelling became too severe at night following injury to allow him to go on without attention. On the following day *x*-ray disclosed a fracture of the first metatarsal bone at the articulation of the internal cuneiform with the first metatarsal bone. (Fracture by direct violence; intra-articular, simple non-displaced variety.)

Case. II. Mr. J. F. G., aged fifty, miner. Old compound comminuted fracture caused by a dinky-car passing over foot. *X*-ray disclosed fractures of the scaphoid, middle and external cuneiform, first and second metatarsal bones, the latter two at their proximal ends, left foot. (Fracture by direct violence; old crushed type which was the result of a compound, comminuted impacted variety with displacement.)

Case III. Mrs. F., aged fifty-two, short stalky woman. Made sudden turn on foot in effort to get away from rapidly approaching automobile. Felt a severe pain and keeled over in a faint. *X*-ray disclosed a transverse fracture about middle of shaft of fifth metatarsal, left foot. (Fracture by indirect violence; transverse and without displacement type.)

Case IV. Mr. M. U., aged forty-two, laborer. Piece of heavy casting fell on right foot. Patient became sick and faint immediately following accident. Severe pain over inner side of foot and rapid swelling with discoloration because patient walked to office using foot after reaction from faint. *X*-ray disclosed longitudinal fracture of first metatarsal bone, right foot. (Fracture by direct violence; variety simple, longitudinal with non-displacement.)

Case V. Mr. S. L., aged forty-two, laborer. Piece of heavy lumber fell across left foot. Became faint and was carried to his home near place of accident. Severe pain, inability to step on toes in effort to walk. Suspicion of fracture of tarsal and metatarsal bones on inner side of left foot. *X*-ray disclosed impacted fractures of the external and middle cuneiform with fractures of the articular surfaces of the third and fourth metatarsals (tarsometatarsal articulation). (Fracture by direct violence; variety simple, impacted, multiple and dentate with non-displacement.)

Case VI. Mrs. P. E. B., aged twenty-four. Turned on right ankle falling down stairs. Experienced a sudden sharp pain and snap. Became sick and vomited upon removal to offices for attention. Prompt swelling thereafter on dorsum of foot. Pain on motion and during palpation, especially marked on the outer margin of right foot. *X*-ray disclosed fracture of the fifth metatarsal bone at its proximal end, inferior surface of the tuberosity. (Fracture by indirect violence; variety simple, incomplete, dentate with non-displacement.)

Conclusion. Immobilize foot in plaster-of-Paris cast for all metatarsal fractures for no less than three weeks. Use foot for full weight-bearing guardedly, beginning with the end of the third week in single and simple metatarsal fractures. Use foot for full weight-bearing guardedly after the fourth week in complicated fractures, however, only after immobilization in plaster cast for four weeks has been carried out, following completion of treatment of the compound fractures. Upon removal of the fixation cast begin prompt massage and movements with hot baths or bakings of foot each day. Crushed metatarsal fractures, although they may frequently demand amputation, may be, in instances of perseverance, spared for subsequent reconstruction work. Thus, there is afforded a better means for establishing a useful supporting extremity. A deformed foot is better than no foot, and reconstruction work affords the opportunity toward making an unsatisfactory initial piece of conservative surgery more satisfactory.

CASE REPORT

COMPLETE DISLOCATION OF KNEE*

EDGAR W. WEIGEL, M.D.

PLAINFIELD, N. J.

THE patient, an auto-mechanic, nineteen years of age, while playing football was tackled from the back and fell; upon arising, he noted pain in the left knee and marked deformity of the knee. He was brought to the hospital immediately, where clinical examination revealed an anteroposterior complete dislocation of the knee, with 3 in. of over-riding of the femur behind the tibia, accompanied by marked swelling and tenderness. Roentgenograms were taken and showed the condition, with no fracture present.

FIG. 1. FIG. 2. FIG. 3. FIG. 4.

One hour after the injury, under gas anesthesia, with considerable difficulty owing to the over-riding, the dislocation was reduced by traction in hyperextension. A well-padded plaster leg bandage was applied, with the knee in full extension. The knee was immobilized for five weeks, the plaster bandage being bivalved at the end of the second week to facilitate treatment with baking and massage. Six weeks after the injury the patient was bearing weight on the extremity, and eight weeks after the injury he was walking without crutches or cane. Three months after the accident he was back at work, doing a heavier and harder kind of work than before the injury, with a pain free knee that was as stable as the other, and with a range of motion that was so nearly complete that only instruments of precision could reveal any difference from the other knee.

DISCUSSION

DR. REGINALD SAYRE: Some two years ago I saw a somewhat similar case of a man who fell through the skylight thinking he was dropping into his own room but instead fell two stories down the stairs dislocating his knee in an almost identical manner as Dr. Weigel's patient. He was taken to Bellevue where Dr. Wadhams snapped the knee into perfect alignment, under ether, and applied a plaster of Paris splint. Four weeks later I applied a Campbell splint to prevent undue lateral mobility while he was walking around. This splint he wore for about a year, doing exercises in the meantime to develop his thigh muscles.

* Read before the Section of Orthopedic Surgery, New York Academy of Medicine, April 19, 1929.

He now has a perfectly practical leg which he can use in driving a car.

Dr. George E. Bennett: This case illustrates a noteworthy point in that you can have a rupture of the anterior crucial ligament and yet have a perfectly good knee joint as the result, provided the other ligaments are intact. There has been too much stress laid upon the importance of crucial ligaments in stabilizing a knee joint. I do not think they are so important as has been thought.

Dr. Armitage Whitman: I should like to reinforce Dr. Bennett's remarks by the account of a case I had with rupture of both crucial ligaments, in which I did a fascial transplantation and got, as far as the crucial ligaments were concerned, a very good result. Unfortunately the patient was an extremely timid sort of person who was so afraid to move his knee that his quadriceps had gone all to pieces. This boy had a very good joint and with a good quadriceps muscle the result would have been perfect. I am inclined to think that with a good quadriceps the importance of the crucial ligaments can be minimized and if we emphasize keeping up the muscular tone of the quadriceps the injury to the crucial ligaments may not be so important as we think.

Dr. L. T. LeWald: In questions of knee joint injuries, Sir Robert Jones has always said that one should look for fracture of the spines of the tibia. Here is a case, however, where the knee joint has suffered the most extreme injury short of avulsion of the leg, and yet there is no evidence of injury to the spines of the tibia.

Dr. E. W. Weigel: We thought that if the crucial ligaments were torn the most likely place would be the attachment to the tibial spine. I don't understand how he could have such a displacement without their being torn. The stability of the knee joint is undoubtedly due to the strength of the musculature.

Dr. Krida: Fresh cases, are never, to my mind, suitable for open operation. I have seen several of these, though not so extreme as this. It is a very brilliant case, but I am convinced that the rôle of the crucial in favorable cases is not so important as in the typical injuries, those in which the internal lateral ligament is first torn and then, if the distorting force be continued there results a tear of the anterior or both ligaments. Such a knee as I have described may have as a late result a general instability of the knee joint. This, so far as I know is not reparable except by repairing the crucial ligament or by inducing ankylosis.

Fig. 5.

Fig. 6.

Dr. Charlton Wallace: I had two patients: one was a jockey who was thrown from a horse. The base of both spines of the tibia was torn off and the crucial ligament along with it. There was considerable fluid in the joint, which was evacuated and treated conservatively, and he made a perfectly good recovery. The other case was that of a man who stepped down a three-foot trench in the dark and ruptured both crucial ligaments. He was treated conservatively with the idea of developing the muscles going down to the leg; if their tone was restored he would get a good functional result, which he did.

Dr. Elmer P. Weigel: It must be that the crucial ligaments at the time of injury were severed and the reason he has such a good knee now is due to his good musculature. I cannot conceive of the ligaments being stretched to that extent without more serious results.

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The American Journal of Surgery is truly independent and enters into no "entangling alliances." It publishes many papers read before the leading surgical societies of the Country, but it is *not* "the official organ" of any organization. Every manuscript is selected by the editors, as worthy of publication—nothing is published merely because "it was read at the meeting."

EDITORIALS

NEEDED—AN ANESTHESIA FOUNDATION

AMERICA is the birthplace of anesthesia; to her belongs the honor and esteem of having made the first discoveries and the public proofs of its wonderful and far-reaching possibilities; world-wide acclaim was ours for bestowing upon suffering mankind this most beneficent and almost priceless boon whereby remedial surgical procedures could be performed without causing the patient pain. The announcements of the early clinics demonstrating surgical anesthesia awoke among the medical profession of the world an enthusiasm for scientific research which can be paralleled only by the published reports of a Pasteur, a Curie, a Roentgen, or a Banting of more modern times.

Yet, strange to relate, it is a rather sad commentary that there does not exist in the United States today a single School or Foundation, *backed by a real, live, scientific research department*, where all the different exemplifications of the anesthetic art are used and taught. Nor is there a proper correlation of ideas concerning the many methods of anesthesia. True it is that one may go to this or that hospital to learn inhalation anesthesia by ether or gas-oxygen, or their combinations; yet, to acquire a knowledge of rectal and intravenous anesthesia, it usually is necessary to go somewhere else; and, to see spinal anesthesia and regional anesthesia demonstrated, again one must visit still other clinics.

Further, there are those who claim that inhalation is the *only* type of anesthesia which should be used, condemning regional and spinal, or other methods. Again, some surgeons and anesthetists will argue that

inhalation anesthesia is entirely passé. And so the turmoil rages, not only regarding anesthetic agents and methods, but also concerning apparatus, paraphernalia, equipment and other allied factors. Nowhere in the United States today is there an outstanding Anesthesia Foundation of such preponderant prestige and such broad-mindedness, *backed by a painstakingly thorough department of research and publicity*, that to it could be referred for solution both the old and the new problems of anesthesia, and from it could come the most trustworthy and unbiased information and judgment.

It is not difficult for even the laity to comprehend the pain and suffering attendant on the inadequate and oftentimes indifferent surgery which was performable in the pre-anesthetic era; yet, it is believed, many surgeons of today fail properly to recognize that largely because of the varied and manifold advances in the anesthetic art has it been possible for surgery to have made the brilliant progress of recent years, all for the common good, for humanity.

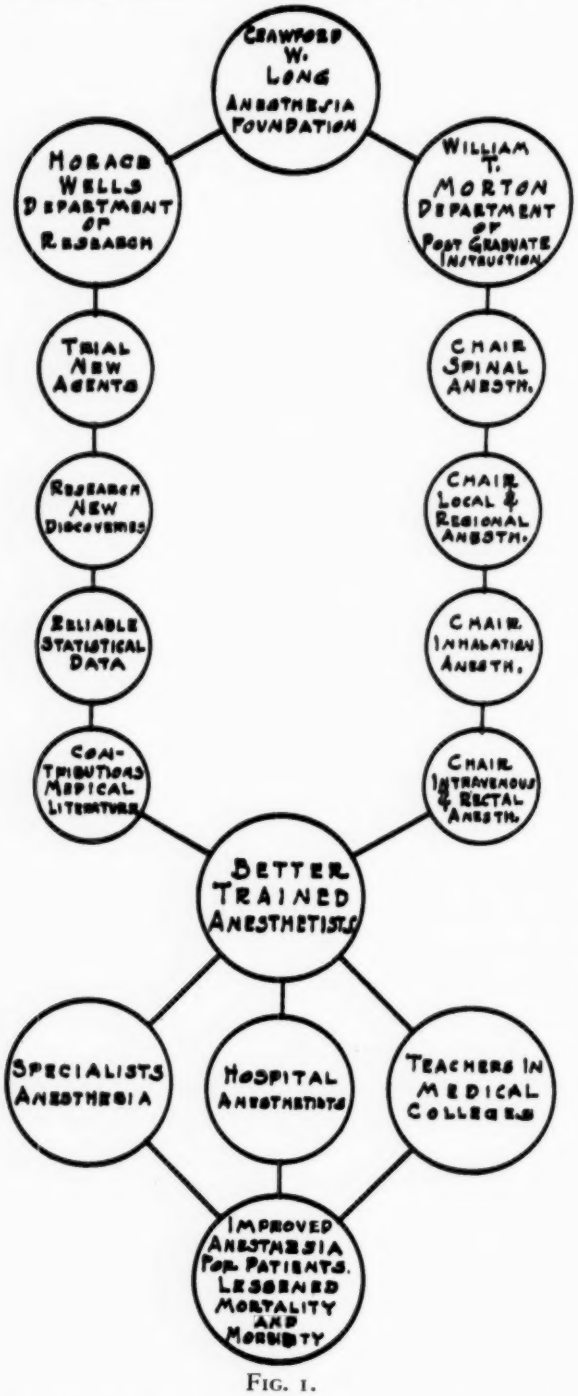
As with many things accepted today as commonplace, as having existed always, anesthesia began in a small way and with a relatively few agents, to blossom forth and fructify into a manifold and ingenious multiplicity of methods, ever keeping step with surgical progress, stride for stride. Too frequently the name anesthetist has been applied to those who understand how to administer but one or two agents and, consequently, every patient and surgical condition were forced to conform to that one type of anesthesia. This is as much in error as trying to fit every individual with the same style or size of clothes, and it is not necessary to visit many clinics to be convinced of the fact that lack of experience in *all* anesthetics often leads to faulty judgment in the attempting to attune *all surgery* to but *one anesthetic*.

Only for the sake of emphasis is it well to review that Dr. Crawford W. Long first used ether in 1842, that Dr. Horace Wells administered nitrous oxide gas to his patients for extractions in 1844, and that Dr. William T. Morton gave the premier demonstrations of ether anesthesia in the Massachusetts General Hospital on October 16, 1846. Since that time a host of agents and methods have proved their worth: by inhalation, ether, chloroform, ethyl chloride, nitrous oxide, ethylene and carbon dioxide; for local and topical application, cocaine, procaine, butin and others; for intravenous injection, sodium amytal; for rectal injection, ether-oil, avertin, and ether-barbital; for regional, procaine and neocaine; for spinal or subarachnoid block, neocaine, novocaine, spinocaine, gravocaine and others. The anesthetist of tomorrow must be proficient with all agents and methods; he must be able to select and adapt each to the individual patient and the particular surgical requirement; this for but one end, that the patient may get well.

Anesthesia as a specialty, in the past, has not attracted its just proportion of the best-trained medical minds; and, in consequence, a sort of medical football, it has been kicked about, often exploited alike by surgeons, hospitals and clinics, all of whom assigned to anesthesia the most minor of rôles, in many cases relegating the work to students, orderlies and nurses, none of whom ever is permitted to administer a single hypodermic of morphine without a physician's express prescription; yet, to them often was handed a mask, with ether can or chloroform flask, and they were told to "just go ahead." This is not, never was and never can be, to the best interests of public weal; and, to overcome and improve just such a situation, to project oneself into the future ten, fifteen or twenty years, to do the real thing for anesthesia in a proper and highly scientific way, to provide the needed increase in trained medical personnel and to give them the necessary foundation, it must be obvious that a parent body, a fountainhead, an Anesthesia Foundation, is a very pertinent, present-day need.

A tentative outline of such a foundation

is herewith submitted. It does homage to those pioneers whose courage of conviction was responsible for the development of the


CRAWFORD W. LONG ANESTHESIA FOUNDATION
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WILLIAM T. MORTON DEPARTMENT OF POST GRADUATE INSTRUCTION
TRIAL NEW AGENTS
CHAIR SPINAL ANESTH.
RESEARCH NEW DISCOVERIES
CHAIR LOCAL & REGIONAL ANESTH.
RELIABLE STATISTICAL DATA
CHAIR INHALATION ANESTH.
CONTRIBUTIONS MEDICAL LITERATURE
CHAIR INTRAVENOUS & RECTAL ANESTH.
BETTER TRAINED ANESTHETISTS
SPECIALISTS ANESTHESIA
HOSPITAL ANESTHETISTS
TEACHERS IN MEDICAL COLLEGES
IMPROVED ANESTHESIA FOR PATIENTS. LESSENED MORTALITY AND MORBIDITY

FIG. 1.

art. No living name should be attached, for apparent reasons; yet its various chairs provide a future place for men now amongst us whose work and research are worthy of acclaim. The ideals of such a foundation should be large, broad; they must transcend even the immediate years. The foundation must be above jealousies and intrigues; its policies must be shaped toward the greatest good for the greatest number; it must be cooperative in every sense of the word with individual research workers everywhere and encourage them; it must be favored and upheld by manufacturers of medical supplies and appliances; it must be backed by a large medical center for clinical material; it must be supported by the medical periodicals; it must have the sympathetic interest of the medical colleges, for it should furnish them with their future teachers. The diagram is practically self-explanatory, excepting those details which are too numerous to include in a preliminary monograph; yet, to mention but a single angle, think of the enrichment of the medical literature, for future generations, which such a foundation would provide?

A dream? Perhaps. A utopia? No! It *can* and *must* be accomplished. The practice of medicine is an ever-progressing science; he who stands upon the right of way of the onrushing train of advancement is likely to be found among the wreckage and debris by the wayside.

Certainly, all this cannot be done in a day, a week or a year; the foundation would be just the beginning of an influence which could and should make itself felt through succeeding generations. The beginning necessarily must be small, but the results are none the less sure; the acorn develops into a sturdy oak under proper environmental influences.

How can this be accomplished? By endowment. The foundation could be made entirely self-supporting; but, for the largest good to the greatest number in the shortest period of time, ample endowment is the surest way. What an opportunity for a city! For a medical center! For an individual! It is hoped that this only too brief presentation may meet a kindly eye, an understanding mind and a sympathetic heart.

FLOYD T. ROMBERGER.

NEW METHODS OF PRODUCING GENERAL ANESTHESIA

A DISTINGUISHED surgeon was recently heard to express the opinion that anesthetic agents of the past caused pathological effects, not in the process of producing anesthesia, but while being absorbed and eliminated. He cited the liver damage caused in the detoxification of chloroform; the lung damage accompanying ether when inhaled; and the rectal irritation resulting from colonic ether. He then went on to imply that future developments in the art of anesthesia lay in the direct introduction of the anesthetic agent into the blood stream.

To a practical anesthetist, this rather fundamental suggestion from a surgical authority proved to be food for thought. The first reaction was one of curiosity as to whether the direct introduction of anesthetic agents into the blood stream by intravenous injection was particularly new. A visit to the library brought forth the following facts. Pirogoff reported, in 1847, a series of cases anesthetized by the insufflation of ether vapor into the rectum. Intravenous ether anesthesia was extensively used by Burkhardt and others previous to 1910. In 1872, Oré reported 51 patients anesthetized by the intravenous administration of trichloracetaldehyde (chloral hydrate) and this drug has been extensively used to produce both sedation and anesthesia when administered by rectum, the latter chiefly by Sternimann who, in 1929, advocated its routine use for producing anesthesia in infants. Previous to 1910, Burkhardt reported considerable clinical experience with the intravenous administration of trichlorisopropyl alcohol (isopral). He used this drug alone to produce anesthesia, and more extensively as a preliminary to the intravenous administration of ether. Mertens used trichlorisopropyl alcohol for rectal instillation usually followed by an anesthetic given by inhalations. In the early years of the present century, Schmedeberg, and later Dreser, did some excellent investigation of alcohol derivatives, and produced and used, clinically, methyl-propyl-carbonyl urethane, an ester of carbamic acid (hedonal). Hedonal was used in England and on the continent to produce anesthesia by intravenous administration as well as by rectal instillation. An extensive laboratory investigation of this drug with favorable report was made by Donald.

Doubtless, the advent of the World War placed a damper on basic research in the development of new drugs in Europe. Since the war, further work on alcohol derivatives has resulted in at least one distinct advance, namely, the production of tribromethanol (avertin) by Willstätter and Duisberg. This drug has received a very extensive clinical application during the past few years. It has been administered both intravenously and by rectum to a very large number of clinical cases and the literature contains many glowing reports of its usefulness.

Marin, in 1929, reported 250 cases anesthetized by means of 96 per cent ethyl alcohol in glucose administered intravenously.

We thus see that the attempt to produce anesthesia by the introduction of drugs through the rectal mucosa or through the wall of a vein, is decidely not new. Probably the lack of permanent enthusiasm for these methods is caused by an inherent fault in the methods themselves. The production of surgical anesthesia involves so close an approach to an interference with vital functions that the method involved should, to be absolutely safe, carry with it a control approaching instantaneous. A drug which can be introduced into the circulation and removed therefrom in a few seconds will always have an appeal to the conservative anesthetist. The use of methods which lack this quality of quick control should probably be confined to a basic preparation for the use of other methods. At the present time, the possibility of the pharmacologists' producing new drugs, which can

be administered in a previously guessed dosage sufficient to accomplish safely complete surgical anesthesia, is very remote.

If a practical anesthetist may be permitted the liberty of suggesting to the experimental chemist and pharmacologist where his future efforts seem likely to be of benefit in anesthesia, it might be stated that further work on derivatives of the alcohols, particularly halogen substitutions with the alcohols, seems to offer the brightest outlook. No barbituric acid derivative has yet been produced which seems to have primarily an anesthetic effect. Many of them produce excellent psychic sedation and are very useful for the production of sleep but in no case has a derivative of barbituric acid been found to be primarily an anesthetic agent. Overdosage, of course, produces a condition simulating anesthesia during which surgical operations can be performed, but the use of such dosage is decidely unjust from the standpoint of safety. On the other hand, many if not most of the anesthetic agents which we now possess are either direct or indirect derivatives of the alcohols.

The greatest need at the present time in the field of general anesthesia is the development of a highly volatile or gaseous substance which will have the labile qualities of nitrous oxide gas with sufficient potency to produce complete relaxation of the abdominal muscles with quick recovery of muscular tone and consciousness when the administration is interrupted. Investigation is being conducted along this line by V. E. Henderson. Such a drug to be used in conjunction with the drugs now available, or to be made available, for intravenous, subcutaneous or rectal administration might approach the ideal.

What can the practical anesthetist in the operating room find of additional value in the newer drugs and methods offered for the production of anesthesia? He will doubtless find a field of usefulness for barbituric acid derivatives in the production of sleep to accompany block anesthesia by means of procaine or its substitutes, and to prepare the apprehensive patient for inhalation anesthesia. He will doubtless wish to choose a barbiturate with a short-lasting effect rather than one which maintains sleep over long periods. A drug which promises something along this line is secondary butyl-brom-allyl barbiturate (pernocton). Ethyl-methyl-butyl barbiturate also gives promise of early detoxification and reasonable stability of dosage. He will doubtless find the rectal administration of tribromethanol advantageous in certain types of cases. The instillation of a bland solution into the rectum to produce sleep in children is highly desirable. Certain individuals, on the other hand, would much prefer an intravenous injection to a rectal instillation. There is little to choose between a barbituric acid derivative and tri-brom-ethanol as inducers of sleep. A quick pleasant "dropping off" is the result.

The anesthetist should bear in mind that new drugs will undoubtedly be produced which are more desirable than those now available, but he should also remember that careful laboratory and animal experimentation must precede their clinical trial. At no time should the fact be lost sight of that the dosage of anesthetic drugs is extremely variable for different individuals, and that a predetermined dose based on body weight, age or any other known factors, is seldom reliable. Particularly is this true of barbituric acid derivatives. Physical signs, alone, can determine the effect of anesthetic drugs. Any drug, therefore, that is administered by rectum or intravenously must be given in dosage short of that necessary to produce complete, deep surgical anesthesia. Completion of surgical anesthesia should be effected by the use of a drug controllable from second to second as the exigencies of the case demand.

Ralph M. Waters.

Henle

JACOB HENLE

[1809-1885]

"THE HENLE TUBULES"

JACOB HENLE was born of Jewish parents at Fürth, near Nuremberg, in 1809. He died, having reached a high pinnacle in science, at the ripe age of seventy-six years.

He was a great anatomist and the foremost German histologist of his day.

He began his scientific life as one of Johannes Müller's most brillant and favorite pupils. Henle was one of his prosectors at Berlin. Later he was professor of anatomy at Zürich (1840), Heidelberg (1844), and Göttingen from 1852 until his death.

Henle's life was a many-sided one and into his years he crammed the accomplishments of several normal existences.

He was the founder of our present conception of the epithelial tissues of the body.[1]

In his "Allgemeine Anatomie"[2] Henle demonstrated the presence of smooth muscle in the middle coat of the smaller arteries. This was the beginning of the present theory of the vasomotor mechanism. In addition, he discovered the external sphincter (striated muscle) of the bladder, the central chylous vessels, the internal rootsheath of the hair, the Henle tubules in the kidney (1862, contained in his "Handbuch der systematischen Anatomie"), gave the first accurate description of the histology of the cornea, and described the morphology and development of the larynx. Henle was the first to demonstrate many important structures of the brain.

During 1838 to 1841 Henle collaborated with Müller in his monograph on the plagiostomes.

He wrote an essay "On Miasms and Contagia" (1840) which contains the first clear statement of the idea of a *contagium animatum*. He elaborated Müller's belief that fever is only a symptom. In his "Handbuch der rationellen Pathologie" (1846–53) he claimed it to be the physician's duty to prevent and cure disease; that all disease is a deviation from normal physiologic processes, and that death is the cessation of metabolism. In 1844 he discovered cylindric casts in the urine.

Henle wrote two books on anatomy. The first, "Allgemeine Anatomie" (1841), was the first treatise on microscopic histology. It contains the simplest and best classification ever made. Later (1866–71) he brought out "Handbook of Systematic Anatomy," a three volume affair, very thorough and highly scientific. Henle did the illustrations for it and said that they are architectural rather than diagrammatic.

Henle was a pleasing and engaging lecturer. As he instructed his students he illustrated his points with clever drawings on a blackboard.

For avocations he dabbled at art, was more than a mediocre poet, and was an accomplished musician, playing several instruments. His first marriage was unusually romantic and seems foreign to the part of a German scientist.

Henle's friendships were many and with the first minds of his time. All in all his life was almost the ideal so many dream of but so few attain. In the midst of his many interests, Henle, an old man, departed from this life in 1885.

[1] Symbolae ad anatomiam villorum intestinalium imprimis eorum apithelii et vasorum lacteorum. Berlin, 1837.

[2] Leipzig, 1844.

[From Fernelius' Universa Medicina, Geneva, 1679.]

BOOKSHELF BROWSING

FLORENCE NIGHTINGALE

ANGEL OF MERCY AND HUMAN DYNAMO*

FRANK K. BOLAND, M.D.

ATLANTA, GA.

FEW speakers at the graduation exercises of nurses' training schools fail to refer to Florence Nightingale, but fewer still give the audience facts about her life and work. The average citizen perhaps knows that she was some kind of a nurse, but not many appreciate the tremendous influence which she has wielded upon the art and science of medicine. It is a welcome obligation placed upon the medical profession to perpetuate her memory, and in this day of belittling biographies to preserve the truth concerning her achievements.

In reviewing her career one is at once struck by the fact that for the sake of humanity and for no personal gain, she voluntarily forsook a life of pleasure and ease to plunge into a whirlpool of hardships and responsibilities which few of either sex could have withstood. She turned her back on wifehood and motherhood, woman's supreme sacrifice.

She was born of English parents in Florence, Italy, in 1820, and lived to be ninety years of age, dying at her home in London, in 1910. She was named Florence after the city in which she happened to be born. Her father's name originally was Shore, but following an English custom, he adopted the name of his wife's uncle, Nightingale, when she inherited his large estate. The acquisition of this fortune enabled Miss Nightingale in later life to put into effect measures which otherwise might have failed. When she needed money for feeding and clothing soldiers, and was unable to obtain all that was necessary from the government, she contributed from her own resources.

She had the advantage of the best education of the day, and certainly possessed more than appears in the college girl of the twentieth century. Not only was she well versed in the classics, but she knew the science of the times. When she entered the Institute of Protestant Deaconesses at Kaiserwerth, Germany, in 1850, for a few months' training in nursing, she already had studied anatomy and physiology. One distinguished gentleman, next to whom she sat at dinner, remarked that he considered her a capital young lady until she floored him with her Latin and Greek.

Florence Nightingale did not care to be a teacher or devote her life to literature; instead she always was interested in the sick and distressed, and felt a call to help them. For a woman of her high social position, or for any kind of decent woman

* Submitted for publication June 16, 1930.

to become a nurse in England eighty years ago, was an unheard-of thing, and required profound conviction and courageous determination. The bulk of nursing in those days was turned over to an inferior class of women generally without training or character, though the modest school at Kaiserwerth was in existence, and Catholic orders gave instruction in the care of the sick, not as a calling, but as part of their religion. Miss Nightingale's first experience was as superintendent of an "Establishment for Gentlewomen during Illness."

Florence Nightingale

The Crimean War in 1854 furnished her the opportunity to render to sick and wounded soldiers service which has become historic. Thereafter military hospitals were converted from bedlams of filth and misery to havens of efficiency and comfort, with the result that soldiers were able to return to duty with the least possible loss of time. This war was fought between Russia on one side, and England, Turkey and other allies on the other side, Crimea being a peninsula in the Black Sea, between Russia and Turkey.

After the battle of Alma, startling stories came back to England as to the horrible state of affairs in the great Barracks Hospital at Scutari, Turkey, so graphically described by Lytton Strachey. The building was overcrowded, and was so old and worn that it was impossible to clean it.

Apparently no preparation had been made for the care of patients. There was little ventilation and less plumbing. The beds were mostly of straw, and many were laid directly upon the floor. The few sheets to be had were of rough canvas, and the men preferred to lie between blankets. There was no hospital clothing, and most of the patients were still in their uniforms, stiff with blood, and often covered with pus and vermin. The food was badly or half cooked, and the very ill patients had nothing they could eat. Cholera and contagious fevers were common. More soldiers died of disease than of wounds, the total death rate being 42 per cent.

The Crimean War taught the nations that soldier patients are entitled to the same treatment as civilians at home, if not better, and Florence Nightingale was the instructress. Sidney Herbert, Secretary at War, one of her closest friends, requested her to gather nurses and supplies and go to Scutari. At the same time she asked permission to do so. Their letters crossed. Thus armed with authority from the English War Office, she reached the scene with her equipment, and there bitterly opposed by military and medical heads, through her sagacity, tact and indefatigable labor, finally she overthrew the old regime, and instituted common sense and merciful methods of handling patients, the result being that the mortality dropped to 2 per cent. Such is the record, but one difficult to understand when we remember that the science of bacteriology had not yet been born. So much more glory for Florence, one of the world's greatest sanitarians. Sir Edward Cook, one of her principal biographers, said that when Florence Nightingale was born a woman, England lost a great commander. She certainly commanded the situation during the Crimean War, and produced results which probably only a woman could have done. What other name has descended to us from this conflict?

The period of the Crimean War was the most dramatic part of Miss Nightingale's long life, and her fame rests chiefly on her epochal achievements at that time. She was then thirty-four years old, and keyed up to the highest pitch of mental and physical energy, but the exposure and strain which she suffered undermined her constitution to such an extent that she was destined the rest of her days for invalidism or semi-invalidism. The exact diagnosis of her trouble has not been given. By some it was called heart disease, by others it was termed neurasthenia. Neither condition, however, could dampen her enthusiasm nor diminish her enormous capacity for work, so that for forty more years she strove effectively, often from a sick bed, for the advancement of hospitals and nursing, both in military and civil life.

She founded modern nursing, as we know it today. She elevated from disrepute what was regarded as a lowly occupation, and made of it one of the most useful and noble of callings. Following her return from Scutari she was the popular idol of England, although she shrank from publicity. A fund of a quarter of million dollars was raised to establish the Florence Nightingale Training School, where scientific nursing was first taught. From this institution her pupils went out to teach the world. She was guilty of one error of omission, in common with many of the older surgeons who were her contemporaries. She failed to accept the germ theory, and did not include surgical antisepsis in her instruction, although she must have witnessed the triumph of Lister's great discovery.

To Miss Nightingale belongs not only the honor of creating a new profession, but also she should be credited with being the first to enunciate the fundamental principles of nursing. These we find proclaimed in her delightful though diminutive "Notes on Nursing." Here we are impressed for the first time with the importance of ventilating a sick-room and keeping it clean and warm. The proper preparation and serving of food are described, and the necessity for quiet is emphasized. Don't

surprise the patient; nothing should ever surprise the patient except a burglar. Don't sit on the patient's bed. Don't awake the patient suddenly out of a sound sleep. Don't compel the patient to crane her neck to see you when you are talking to her. These and many other commonplace rules have guided nurses ever since Florence Nightingale first put them into writing. "Notes on Nursing" is a treasure-house for all those who are entrusted with the care of the sick.

Of the numerous poems dedicated to this genius, Longfellow's "Santa Filomena" perhaps is the best known. Beautifully he writes:

Lo, in that house of misery,
A lady with a lamp I see
Pass through the glimmering gloom,
And pass from room to room.
And slow, as in a dream of bliss,
The speechless sufferer turns to kiss
Her shadow as it falls
Upon the darkening walls.

Not always did Florence fill the gentle picture suggested by these lines. How could she when she subdued the stern colonels at Scutari, so amazed by her presumption? How could she be mild when in later years she coped so successfully with the leading politicians of the day? With her culture and refinement she could be as sympathetic and charming as the best. Sympathy for suffering mankind was the basis of all her efforts. To carry out her exalted plans, however, demanded driving power, often felt by her friends almost to the breaking point. To overcome obstacles her methods at times might today be characterized as "hard-boiled." Rare executive ability and keen knowledge of human nature were two of her greatest assets. She had vision in advance of the age, and lived to see most of her dreams come true. The world of medicine and all humanity must ever pay homage to Florence Nightingale.

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BOOK REVIEWS

Creed of a Biologist. By Aldred Scott Warthin, M.D., 60 pp., N. Y., Paul B. Hoeber, Inc., 1930.

It is refreshing to read the philosophical convictions and beliefs of one who has attained unusual success and eminence in more than one field of endeavor. Dr. Warthin is known as an exceptional teacher. He is recognized as one of the foremost pathologists of this day and age.

And so, after years of teaching undergraduates, moulding their minds and characters, after decades of delving into the deeper recesses of medical lore, after the widest kind of clinical contact with suffering humanity, this student and lover of the arts and mankind, has translated the convictions resting in his soul for others to read, ponder, and digest.

In this age of extremes when it is customary for pseudo-scholars to go off half-cocked and lay down a dogma built on false premises, it comes to one as a breath of cooling fresh air at the close of a hot, sultry day to read, and read again and again, the pages of this small book. You may not agree with the writer of the pages. But you will be stimulated and it may help you, as it is sure to help many others, to reason out your own philosophy.

It is one of the true books, a book every physician should read many times and digest, a book that comes to one's attention only at very long intervals of time.

Physiology and Biochemistry in Modern Medicine. By J. J. R. Macleod, M.B., LL.D., D.Sc., F.R.S. Assist. by Roy G.

Pearce, A. C. Redfield, N. B. Taylor, J. M. D. Olmsted and by others. Ed. 6. 1107 pp., 295 illus., including 9 plates in colors. St. Louis, C. V. Mosby Co., 1930.

This book which was first published in 1918 and now appears in its sixth edition, has definitely taken its place as one of the classics of medical literature. As the author points out, "Steady increase in general knowledge, rather than discovery, has been the feature of the advances in physiology during the past three years." It has been well stated that to know modern physiology is to know medicine and surgery and if this be true then there is no better volume to have on hand for reference than this work of Macleod's.

Great Painters and Their Works As Seen By A Doctor. A series of monographs ed. by Dr. J. G. De Lint. 1. Rembrandt. Dr. J. G. De Lint. 113 pp., 64 illus., The Hague, J. Philip Kruseman.

This book presents a new viewpoint. It is the first of a series, the purpose of which, according to the author, is "to analyse works of the Dutch painters of the 17th and 18th centuries and to notice what they contain of medical interest." This volume is divided into eleven chapters with such titles as Physicians and Quacks, Portraits of Physicians, Anatomy, Internal Medicine, Miraculous Healings, Surgery, Ophthalmology, Lying-in Room and Care of Infants, and it is illustrated with sixty-four splendid reproductions of the artist's paintings and etchings. Such a study of the work of these artists cannot but be a great addition to the cultural side of medicine. Garrison and others have previously pointed out the value, from a historical medical point of view, of the observations made by the old masters and to have a thorough study on this subject made by a scholar like Dr. De Lint is an event to be welcomed by those interested in Medical History.

A Synopsis of Surgery. By Ernest W. Hey Groves, M.S., M.D., B.Sc. (Lond.), F.R.C.S. (Eng.), Ed. 9, 674 pp., Illus. N. Y., Wm. Wood & Co., 1930.

Nine editions and twelve printings since 1908 are evidence that this book has stood the test of time. Thoroughly practical, well done and arranged for quick reference, the work belongs on the five foot book shelf of every surgeon. This edition has been largely rewritten and brought up to date. As evidence of the thorough presentation of the subjects treated the preliminary paragraph on spinal anaesthesia may be quoted: "Although the scope of this method is not nearly so great as it promised to be on its introduction, it has undoubtedly a most valuable place among anesthetics. It is impossible, however, yet to decide what is its mortality compared with general anesthesia, because: (a) many thousands of cases are necessary for comparison; (b) spinal anesthesia, in this country at any rate, is limited to cases of special gravity, whilst general anaesthesia is used for all trivial operations. Hence, what follows must be accepted with the limitations here suggested."

Collected Papers of the Mayo Clinic and the Mayo Foundation. Ed. by Mrs. M. H. Mellish, Richard M. Hewitt, B.A., M.A., M.D., and Mildred A. Felker, B.S., Vol. XXI, 1929. 1200 pp., 279 illus., Phila., W. B. Saunders Co., 1930.

The editor states that for this volume "There were 471 papers from which to make selections. Of these, ninety are reprinted in full, twenty-three are abridged, sixty-eight are abstracted, and to 290 references only are given." When it is realized that the 1200 pages represent only a small portion of the work done at this clinic in one year, an idea may be obtained of the tremendous amount of work turned out at Rochester. The editing, as always, is well done and this volume like the previous ones in the series is a distinctive contribution to surgical literature.

Surgical Diagnosis. Vols. I, II, III, and Index. By American Authors. Ed. by Evarts Ambrose Graham, A.B., M.D., 2907 pp., 1250 illus., Phila., W. B. Saunders Co., 1930.

The Editor states that: "In preparing this work on Surgical Diagnosis an effort has been made to construct a book which will be helpful not only to the surgeon but to his medical colleagues as well." It is to be hoped that many medical men will read this work.

The subjects are treated completely and without padding. The illustrations, which are numerous and useful, have been well selected. The contributors include the leading men of the day. It is interesting to note in comparing this new system with the older ones, the large number of new men who have been developed during the last generation and who have made a name for themselves in their respective subjects. The Editor and his authors are to be congratulated on the fact that they have adhered strictly to their subject as indicated in the title. "Surgical Diagnosis" is the key-note of the work and it will probably be looked to as the standard on this subject for some time to come.

In a composite work of this kind it is usually possible to select points here and there that are not quite up to the mark. These volumes are so good on the whole that it would be a work of supererogation to pick flaws.

Minor Surgery. By Arthur E. Hertzler, M.D., and Victor E. Chesky, M.D., Ed. 2. 602 pp., 475 illus., St. Louis, C. V. Mosby Co., 1930.

According to the Preface "this book is wholly to aid the dispensary student to understand what he sees in his daily work and to enable him to gain a general perspective of the subject which may be only partly illuminated by his clinical observations." The fact that a second edition has been called for within three years would indicate that this object has been attained. The authors frankly state that no attempt has been made to include methods not used in the Halstead Clinic. For this reason detailed criticism would be unfair as would also be discussion as to what is included or omitted in a volume on "Minor Surgery." This work is the expression of Dr. Hertzler's ideas and as such it is stimulating and of great interest.

Syphilis Héréditaire du Système Nerveux. By L. Babonneix. 432 pp., 54 illus., Paris, Masson et Cie, 1930.

The old question of hereditary and syphilis is discussed in detail in this 432 page book. The subject is well covered, with a final chapter on treatment that is practical and up-to-date. As is unfortunately true of most French books, there is no Index but a fairly good Table of Contents.

Physikalische-chemische Probleme in Der Chirurgie. Von Dr. C. Häbler. 284 pp., 62 illus., Berlin, Julius Springer, 1930.

The author is in the unusual position of having put in many years in the physiological laboratory followed by extensive experience as a practical surgeon. He is, therefore, well equipped for the production of this volume, which will be found an invaluable guide to modern methods of investigation by every German reading surgeon. It is to be hoped that an equally thorough study of the subject will soon be made available in English.

Dedication of the Montgomery Ward Memorial Building. Northwestern Univ. Medical School. Alexander McKinlock Memorial Campus. 203 pp., Illus. Chicago, 1929.

This is a splendid volume edited by Irving S. Cutter, Dean of Northwestern University Medical School. It is divided into five parts:

Part One is Introductory and tells of Mr. Ward and other contributors to Northwestern University Medical School. Part Two gives the history of the school and Part Three tells of the opening of the Archibald Church Medical Library and the unveiling of twelve portraits in connection with these ceremonies. There is also the story of the dedication of the Departments of Pathology, Bacteriology, Physiology and Anatomy. Part Four is headed "General Addresses" and begins with the "Problems in Medical Education" by Charles H. Mayo.

Part Five has a special collection of papers headed "Scientific Presentations." These papers are models of concise, well edited "theses" and are exceedingly well illustrated.

OBSTETRICS FOR NURSES

A Syllabus of Lectures on Obstetrics for Nurses has been prepared by a Committee appointed by the American Gynecological Society and is now ready for distribution to those interested in the subject of nurse training. Copies may be obtained from the Chairman of the Committee, at the nominal price of fifty cents by addressing a request to 23 East 93rd Street, New York City.

PROGRESSIVE MEDICINE. A Quarterly Digest of Advances, Discoveries and Improvements in Medical and Surgical Sciences. Ed. by Hobart Amory Hare, M.D., LL.D. Assist. by Leighton F. Appleman, M.D. Vol. II. 416 pp., 54 illus., Phila., Lea & Febiger, 1930.

The contents of this volume are as follows: Hernia; Surgery of the Abdomen, Exclusive of Hernia; Gynecology; Disorders of Nutrition and Metabolism; Diseases of the Glands of Internal Secretion; Diseases of the Blood and Spleen; Ophthalmology. The subjects are presented in concise, readable and up-to-date form.

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A CLINICAL STUDY OF THE ABDOMINAL CAVITY AND PERITONEUM

EDWARD M. LIVINGSTON, M.D.

PUBLISHED SERIALLY IN

The American Journal of Surgery

SEVENTH INSTALLMENT

SECTION II. THE GASTROINTESTINAL TRACT (CONTINUED)

[In the following pages the Journal page number will be found at the bottom of the page.]

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A CLINICAL STUDY OF THE ABDOMINAL CAVITY AND PERITONEUM

Section II. The Gastrointestinal Tract

A. BASIC EMBRYOLOGICAL CONSIDERATIONS (*Continued*)

2. The Origin of the Peritoneal Cavity. A description of the development of the peritoneal cavity, stated in broad terms and without regard to details, is as follows: The embryo (Gr. *embryon*, a rudiment; the product of conception during the first three months of intrauterine life) first consists of a flat structure known as the disc, plate or embryonic streak. This is composed on its dorsal surface of a layer of ectoderm and on its ventral surface of a layer of endoderm (Fig. 101A); between these primary layers there subsequently appears a mass of mesoderm, and the earliest suggestion of the future peritoneal cavity is seen when on each side of the midline this mesoderm splits into two layers leaving between a cleft or space (body cavity or celom). (Fig. 101B). As the embryo subsequently changes from its original flat shape and becomes transformed into a cylindrical structure, these two lateral clefts approach one another ventrally (Figs. 101C and D) where they finally fuse in the median plane, completing, thereby, the closure of the gastrointestinal tract, the formation of the anterior abdominal wall and the creation of the celomic or peritoneal cavity (Fig. 101E). The abdominal portion of the body now consists, as previously described, of a tube suspended within a tube (see formation of gastrointestinal tract). The inner tube (bowel) is attached to the outer tube (body wall) by suspending masses of mesoderm which are situated in the median plane. The attachment running to the bowel from the posterior abdominal wall is termed the primitive dorsal mesentery and the attachment passing to anterior surface

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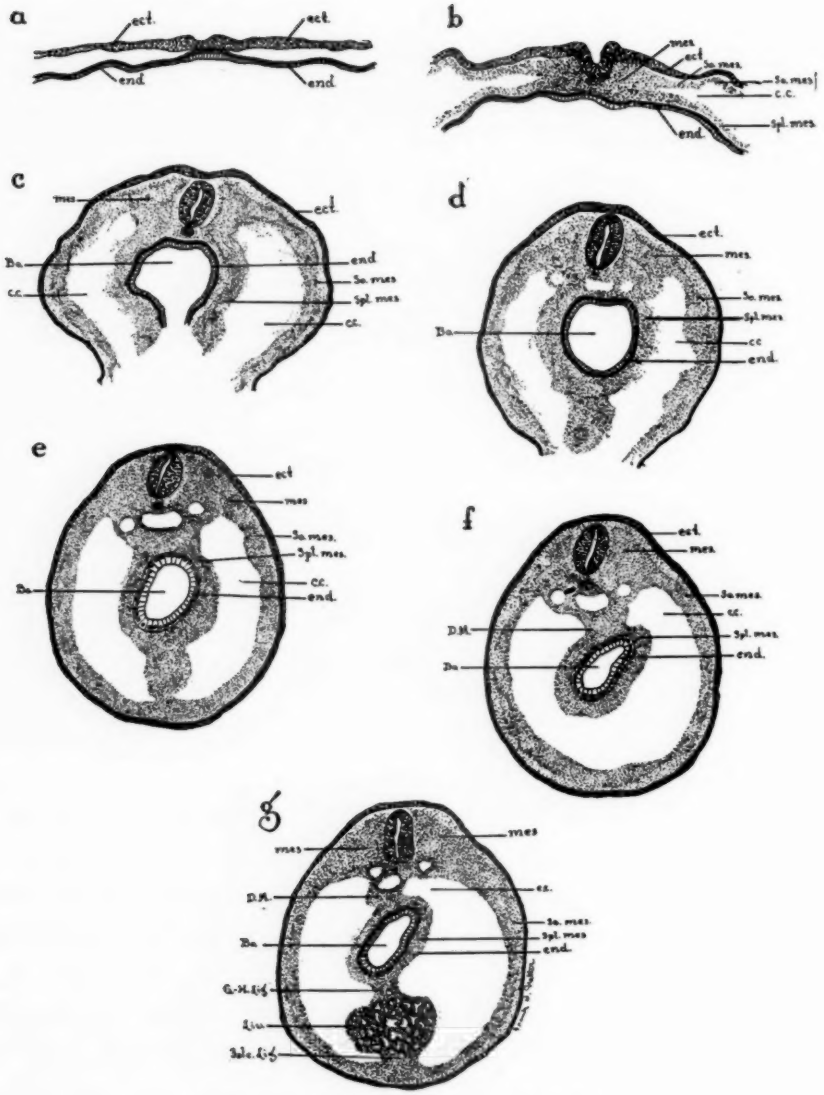


FIG. 101. Origin of peritoneal cavity.

a. The embryonic rudiment (flat structure) situated between the amnionic cavity (ectodermal) posteriorly and the yolk sac (endodermal) anteriorly.

b. Later stage showing mesoderm with the mesodermal clefts which represent the earliest evidence of a future peritoneal cavity.

c. These mesodermal clefts, formed by the splitting of this germ layer into the splanchnic and somatic mesoderm, approach one another as the embryo grows forward to form the anterior abdominal wall.

d. Later stage in which the endodermal layer has fused to form the enteric canal.

e. Still later stage in which the ectodermal layer has also fused, forming the anterior body wall. The peritoneal cavity is enclosed between bowel and body walls.

f. Cross section below level of umbilicus. The inner tube (bowel) is suspended by a dorsal mesentery within the outer tube (body wall).

g. Cross section above level of umbilicus. Here the bowel is supplied with a ventral as well as a dorsal mesentery. Note developing liver within the ventral mesogastrium.

ect, ectoderm; end, endoderm; mes, mesoderm; so. mes., somatic mesoderm; spl. mes., splanchnic mesoderm; c.c., celomic cavity. bo., bowel lumen; d.m., dorsal mesentery; g.h. lig., gastrohepatic ligament; liv., liver; falc. lig., falciform ligament.

of bowel from the anterior body wall is termed the primitive ventral mesentery (Fig. 101F). Below the level of the umbilicus no ventral mesentery exists so that here anteriorly the space is undivided (celomic or peritoneal cavity; Fig. 101G). But above the umbilicus this ventral mesentery persists and here the peritoneal cavity always remains more or less divided (see falciform ligament of liver).

The peritoneal cavity is the result, then, of a splitting of mesoderm as this germinal layer divides to adhere in part to the alimentary tube (splanchnic mesoderm) (Gr. *splanchnon*, a viscus); and in part to the outer wall of the body (somatic mesoderm) (Gr. *soma*, a side). And the flat cells which line the cavity and cover the peritoneal membrane are derivatives of primitive mesoderm (the endothelium).

This simple arrangment of the gastrointestinal tract, body wall and peritoneal cavity represents the final state of affairs with certain lower forms of life, but in the body of the human many subsequent changes take place. These are so numerous and complex that to clearly comprehend the manner in which the abdominal viscera ultimately are related to one another and to the body walls constitutes a somewhat difficult task. This task is simplified by recalling that the many ligaments, peritoneal folds, mesenteries and omenta attached to the adult gastrointestinal tract and its outgrowths (digestive glands) *all* are derived from the primitive, simply-arranged ventral and dorsal mesenteries previously described. Were it not for a knowledge of embryology, which makes it possible to trace step by step the changes leading up to final intra-abdominal arrangements, it would prove difficult for the surgeon to possess a satisfactory understanding of the structures with which he must deal upon entering the abdomen.

The attachment, for example, between liver and anterior abdominal wall (falciform ligament), adhering to the embryonic arrangement, lies within the sagittal plane of the body; but the attachment of liver to stomach (gastrohepatic ligament or lesser omentum) lies at right angles to the sagittal plane.

The relationship of these peritoneal folds is readily and simply explained by the rotation of the stomach (90°) which carries the gastrohepatic omentum to a transverse plane (see rotations within the gastrointestinal tract). Similarly the adequate comprehension of many details concerning intra-abdominal structure and organization depends upon an understanding of normal processes of development. Why are some portions of the intestinal tube firmly adherent to the parietes while others are freely movable? How does it come about that many feet of small bowel ultimately are suspended from but 6 in. along the posterior wall of the abdominal cavity? Why does the superior mesenteric artery cross over the terminal portion of the duodenum? Why do not the voluminous intestinal loops more often become entangled? What explanation is there for the fact that the root of the transverse mesocolon overlies many structures rather than is attached directly to the parietes?

Obviously a surgeon possessing clear insight into the modus operandi through which final arrangements in the abdomen are produced is in a position to know how he may safely proceed while operating (in mobilizing portions of bowel; in avoiding important vessels; in relieving intestinal obstructions; in reducing internal hernias; in segregating segments of intestine or creating short-circuits in the alimentary canal); he is qualified to recognize congenital arrests in development when such are encountered; he can differentiate bands and peritoneal folds which represent normal variations, from those which are abnormal formations; and he can judge with reasonable accuracy when intra-abdominal conditions are, and when they are not, consistent with good functional activity. And the diagnostician is aided no less than the operator by a thorough understanding of developmental details.

Under the headings "The Distribution of the Adult Gastrointestinal Tract" and "Final Attachments of the Gastrointestinal Tract" the attempt is made briefly to deal, by means of an embryological approach, with salient points concerning

adult anatomy. Here, as elsewhere, basic subjects are reviewed for the sole purpose of introducing practical surgical topics. Before proceeding to these new headings a few clinical matters will be dealt with which are based upon the origin of abdominal tissues from the three embryonic germ layers.

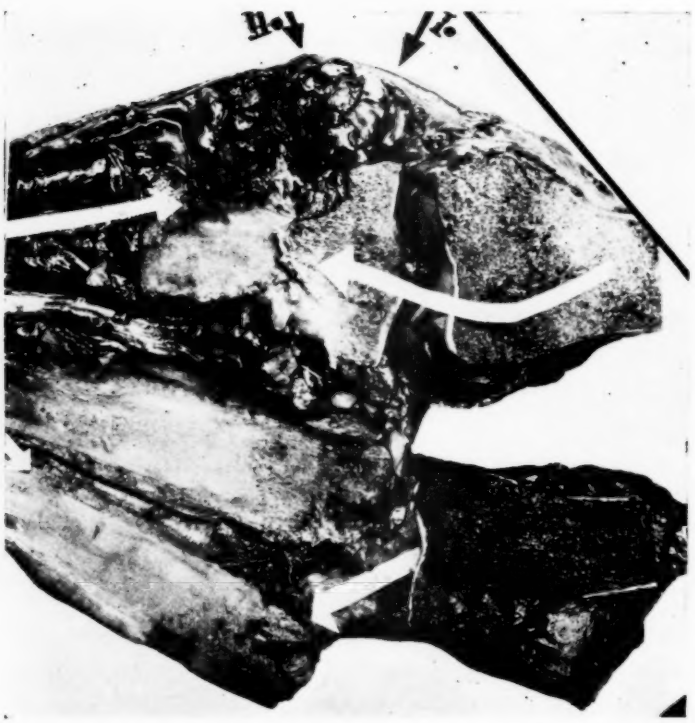
Specific examples of the clinical significance of these germinal layers are readily found in the field of oncology. Malignant neoplasms are at present classified largely upon the basis of the tissues from which they arise; two major groups of malignancies are the sarcomata (malignant tumors arising from mesoderm) and the carcinomata (malignant tumors of epithelial origin). At times malignant ulcers of the two types may be differentiated by simple inspection of the ulcer margins. A sarcoma, as a rule, seems to burst through the skin; it simulates a cannon ball pushing through the integument; it appears to be popping-out at the surface; the surrounding skin margins are thined out; the actual surface ulceration is produced through pressure necrosis while the epidermis itself is never directly infiltrated by the neoplasm, for sarcomatous tissue and epidermis are of totally different germinal origins and the surface involvement is only secondary and indirect (Fig. 102A). With a carcinoma, on the other hand, the skin is unquestionably directly involved by the malignancy; the ulcer margins are hard and thickened; they present a rolled-out appearance which is characteristic; the carcinoma has eaten its way to the surface through a direct involvement of intervening tissues and the skin may appear dimpled, retracted, thickened, puckered and plainly implicated even before the occurrence of ulceration; the situation here represents a tumor within ectodermal tissue spreading throughout more ectodermal tissue (Fig. 102B).

Differentiating Malignant Ulcerations

In dealing with tumors of the abdominal walls such distinctions may prove useful in differentiating desmoids (mesodermal origin) from epitheliomata or other ectodermal newgrowths. (For desmoid tumors see page 98.) A desmoid is rounded or ovoid in shape and the skin is approached,

Desmoid Tumors vs. Epithelial Newgrowths

A



B

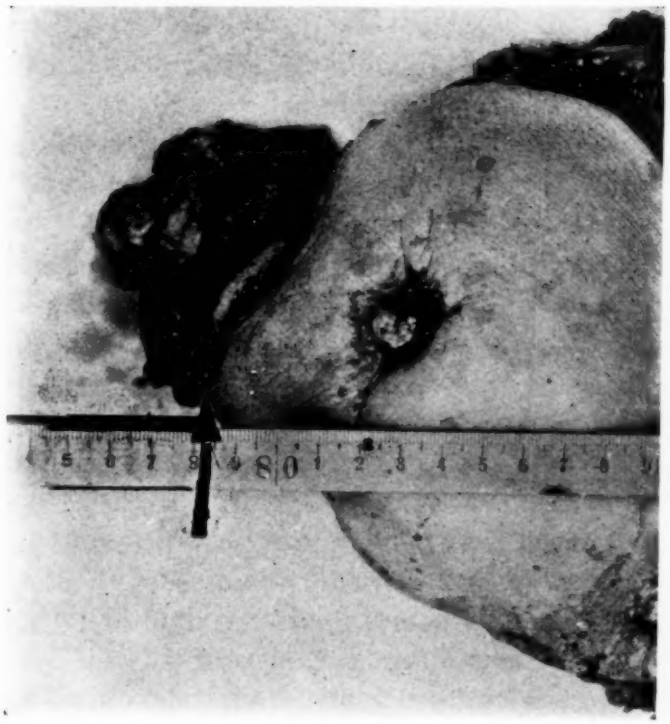
FIG. 102 A and B. Sarcoma, a mesodermal neoplasm pushing through ectoderm.

A. The new growth seems to burst through the skin. The epidermis is not involved except by pressure necrosis.

B. Same growth. Note the thinning out of the integument (1) as the malignant tissue (11) reaches the surface.

(From the Third Surgical Division, Bellevue Hospital, N. Y.)

C



D

FIG. 102 C and D. Carcinoma, an ectodermal neoplasm invading more ectoderm.

C. Note rolled-out margins of malignant ulcer with obvious involvement of the epidermis.
D. Note thickened, rolled-out or everted skin margins at points where the carcinomatous tissue has reached the surface.

(From the Third Surgical Division, Bellevue Hospital, N. Y.)

as the tumor enlarges, by a surface which is convex, or mound-shaped; the abdominal epithelial surface may be encroached upon but will not be infiltrated by the mesodermal neoplasm. In case of a carcinoma of the abdominal wall the tumor is broad or irregular in shape and the external body surface, if not actually involved from the start, is infiltrated early and by a crab-like extension of the process the skin involvement becomes widespread. From these clinical distinctions it is apparent to the examiner that the desmoid is a neoplasm arising in tissue derived from mesoderm and that the carcinoma deserves its characterization as a malignant tumor arising from epithelium (ectoderm).

Peritoneal Neoplasms

Tumors encountered within the peritoneal cavity are more often malignant than benign.[133] But the vast majority of malignancies of the peritoneum are secondary (extensions, transcelomic transplants or metastases from primary tumors of stomach, breast, rectum, uterus, prostate, bile passages, kidney, pancreas; (see malignant peritonitis, p. 192). Primary malignancies of the peritoneal membrane itself are exceedingly rare. Attention will here be focused upon these rare tumors, however, since their occasional occurrence must be kept in mind by the surgeon, who should be familiar with their appearances and manifestations in order to attempt the important differentiation of these uniformly fatal growths from conditions which they tend to simulate (chronic inflammatory exudates, infectious granulomata, pseudomyxoma peritonei). At present there will be excluded from consideration, then, not only the relatively common secondary neoplasms but also the tumors which arise from retroperitoneal tissues (malignant and benign growths springing from lymphatic glands, connective tissue, remains of Wolffian bodies or Mueller's ducts, accessory adrenal bodies); these sometimes grow into the peritoneal cavity in such a fashion as to give the appearance of arising from peritoneal membrane itself and to render the gross differentiation from primary peritoneal malignancies difficult, particularly where the rapid

growth of the retroperitoneal mass into the non-resistant cavity has caused the formation of a pedicle at the peritoneal surface.[134] (For a review of retroperitoneal tumors see Section IV.)

From a study of the germinal origin (embryological development) of the peritoneal cavity (mesoderm) it is seen that primary malignancies of peritoneum must be either endotheliomata or sarcomata. These growths must arise from (1) the endothelium of the serous surface, (2) the endothelium of lymphatic spaces or vessels, or (3) the subserous supporting or connective tissue; all of these are derivatives of mesoderm. Few, if any, tumors have yet been described which could be said to have certainly sprung from the surface cells of the peritoneal membrane, but by the majority of authors primary newgrowths of the peritoneal membrane are regarded as endotheliomata derived from the flat cells of the lymph spaces or lymphatic vessels of the peritoneum. These endothelial malignancies show a marked tendency to a secondary formation of new fibrous tissue (i.e.) they display definite sarcomatous tendencies).[135] The terminology for the tumors has been most varied and this is an index as to the variability of the cellular elements which have been observed in different tumors of this type (malignant lymphangiomata; angiosarcomata; plexiform lymphangiosarcomata or endotheliomata,

Primary Malignancies of Peritoneum

But the surgeon is less interested in details of histogenesis and terminology than in clinical appearances and potentialities. In the main, primary malignancies of the peritoneum may be said to be of 3 chief clinical types; (1) those characterized by a diffuse, shaggy, infiltration of the peritoneal surface at the involved site and closely resembling chronic inflammatory exudates; (2) those characterized by multiple miliary translucent nodules closely resembling the lesions of miliary tuberculosis; and (3) those characterized by the association of villous or papillary elevations with multiple cysts, usually of small size, distributed, often widely, over the peritoneum covering the viscera and parietes.

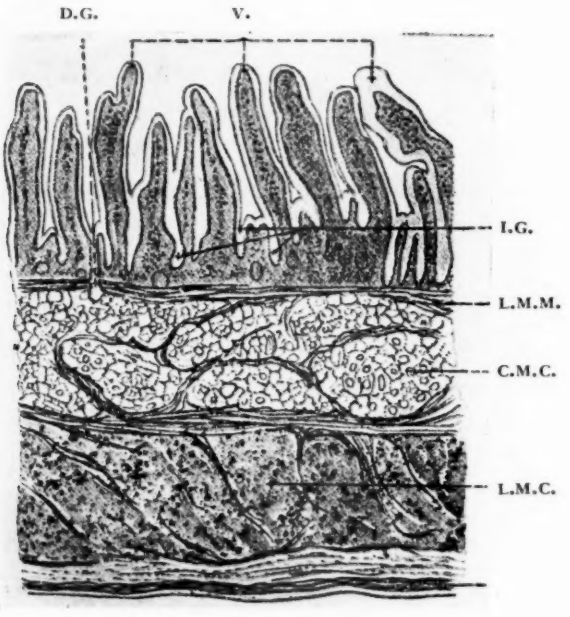
At times the lesions are highly characteristic and the peritoneum everywhere is covered by these tiny nodules, plates, papillary or villous elevations, or again by small malignant cysts, with or without associated solid nodules; the diaphragm may be perforated by the process and the pleural surfaces involved, or the pleura may be simultaneously involved by endotheliomata without gross perforation of the midriff.[136] Single endotheliomatous nodules may fuse and adjacent layers of peritoneal membrane become adherent. Particularly where the cystic variety of tumor is encountered, do universal adhesions tend to develop, together with marked thickening of mesentery and omentum. It has frequently been observed that endotheliomata seem to spring from many peritoneal sites simultaneously, a circumstance in which they thus vary from carcinomatous lesions. Diagnosis is difficult and usually is arrived at only by the process of exclusion. The tumors may be unexpectedly encountered during explorations conducted because of vague abdominal signs and symptoms, or they may be accidentally discovered in the course of operations for other conditions. The presence of a bloody peritoneal fluid is of great significance and should always excite suspicion of malignant peritonitis. Primary malignancies are distinguished from the secondary variety by the finding of the primary tumor or, in its absence, noting one of the characteristic pictures already described. The absolute differentiation of a primary newgrowth of peritoneum from a chronic inflammatory exudate or from a tuberculous peritoneal lesion can sometimes be made only by microscopic examinations. The importance of securing fragments of excised tissue for laboratory examination, and of saving the bloody fluid for the identification of its contained cells, can scarcely be overstated. The differences in prognosis with the different lesions are so great that there seems no excuse for completing an operation in which doubt remains without obtaining material to be submitted to a competent pathologist. Instances have been reported in which, after abdominal closure for a

supposed[1] primary malignancy, not confirmed by microscopic examination, the patient has recovered. Proved primary malignancies are uniformly fatal; no effective treatment by rays, injections or operations has been discovered.[137] Treatment, then, is simply supportive, palliative and symptomatic. Rapid emaciation is the rule. The average life expectancy after the onset of symptoms with primary malignancies of the peritoneal membrane is but eight and a half months.

Germinal Origin of Abdominal Structures

The importance of the germinal origin of any tissue is sufficiently great to warrant a tabulation or summary of the relationships, on this basis, of all abdominal structures. From ectoderm are derived[138]: (1) The epidermis of the abdominal walls and epidermal derivatives, hair, epidermal glands; (2) all abdominal nerves and nervous elements, vagi, sympathetic ganglia and fibers, cerebrospidal nerves, adrenal cortex, chromaffin bodies. From endoderm are derived: (1) The inner lining (epithelial lining) of the digestive tract and its derivatives, duct systems of liver and pancreas; (2) the epithelium (inner living) of the bladder. From mesoderm are derived: (1) The lining membrane of the serous cavity (peritoneum); (2) all muscles, both the striated variety in the abdominal walls and the smooth variety found in the walls of intestines and ducts; (3) all connective tissues, areolar, fibrous, fatty; tendons, ligaments, fascias; (4) all vessels of the circulatory system, veins, arteries, capillaries, lymph vessels and spaces; and also the blood and lymph themselves; (5) the kidneys and ureters; (6) the internal organs of reproduction.

The intestine, then, has an inner lining of endodermal origin, an outer lining (muscle, serosa) of mesodermal origin and nerves and plexuses of ectodermal origin (Fig. 103). The liver has a duct system derived from endoderm, nerve elements of ectoderm and a cellular, capsular, and supporting portion of mesodermal origin. In this way the germinal layers from which the tissues of each viscus spring may be easily recalled and visualized.



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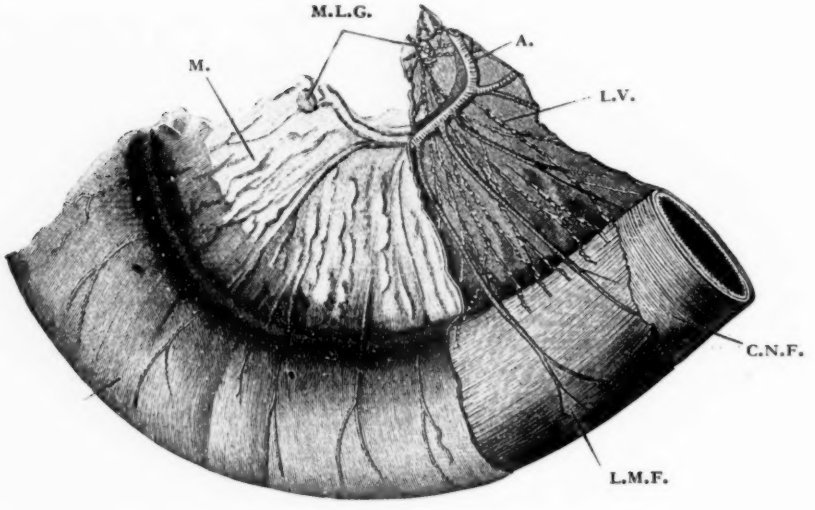

B

FIG. 103 A and B. Structure and coats of bowel, showing development from three embryonic germinal layers: From ectoderm, the nerve elements. From endoderm, the mucous lining. From mesoderm, the peritoneal layer, muscular layers, vessels, fibrous and areolar issues. (From Cunningham.)

D.G., orifice of duodenal gland of Brunner; V., villi; I.G., intestinal glands of Lieberkuehn; L.M.M., lamina muscularis mucosae; C.M.C., circular muscular coat; L.M.C., longitudinal muscular coat; M., mesentery; M.L.G., two mesenteric lymph glands; A., artery; L.V., lymph vessel; C.M.F., circular muscular fibers; L.M.F., longitudinal muscular fibers.

By knowing the germinal origin of a tissue the clinician is in a position to predict with fair accuracy not only the types of newgrowth to which it is liable, but also its general functions; how it will respond to various stimuli (chemical, electrical, psychic), and many other broad considerations of great moment. Abdominal organs or parts of organs, which spring from a common germinal ancestry display similarities and affiliations as such relationships imply. Widely distributed throughout the abdomen, for example, are found small, independent, encapsulated collections of cells of ectodermal origin which have in common the fact that they stain yellow or yellowish-brown in the presence of chromic salts; these are collectively called chromaffin bodies and they, together with cells of the adrenal medulla which take the same stain, are referred to as the chromaffin system.[139] Histogenetically these chromaffin staining tissues are closely identified with the ganglia of the sympathetic nervous system. And the functional similarities between the sympathetic ganglia and the adrenal medulla are well-known (see Visceral Neurology). Interrelationships of the most profound importance between skin, spinal ganglia, sympathetic ganglia, and chromaffin system (all ectodermal derivatives) will later be reviewed, and throughout the text numerous subjects will be found more readily understandable as the surgeon recalls the embryological origin of the tissues involved and the manner in which they are related to other tissues of the body.

The Chromaffin System

Through his knowledge of tissue relationships the broadly trained clinician is in possession of a sound basis upon which to interpret much otherwise unrelated data gathered from the spheres of the many specialties. The basic laws of nature are few. And these tend to be essentially simple. The various actions throughout the body, for example, of adrenalin, pituitrin, thyroxin, pilocarpine, and other drugs might prove difficult even to memorize were it not for the generalizations made possible through knowledge of tissue origins and similar tissue functions. It is a truism that the body is a functional

The General Practitioner and the Specialties

unit, not a series of unrelated parts. And while specialists (the gynecologist, proctologist, cardiologist, ophthalmologist, etc.) are familiar with many facts concerning individual tissues within their respective fields, gained through first-hand observation and representing the accumulated experience from handling vast numbers of cases, the competent general practicioner or diagnostitian, though totally lacking in prolonged and extensive experience in each special field, is able, through the use of analogies and the application of broad principles, to become well versed as to local conditions and to understand his patient as an entity. The specialist offers the patient advantages of detailed knowledge and a high degree of technical skill within a limited field, but it is the general clinician who protects the patient both from study or treatment from a limited point of view, and retains that broad perspective and understanding so essential to unbiased judgment as to the best interests of his patient as an individual.

Since adjacent intra-abdominal tissues are sometimes totally unrelated while those situated at a distance from one another may spring from a common source, it proves advantageous, for numerous reasons, that the practical surgeon bear in mind, and frequently review, the germinal origins of the tissues with which he deals.

3. The Distribution of the Adult Gastrointestinal Tract. In reviewing the manner in which the enteric canal is normally arranged within the abdominal cavity the following points will be taken up in the order named: (a) the rotation of the stomach; (b) the position of the duodenum; (c) the formation of the duodenojejunal juncture; and (d) the rotation of the intestines.

a. Rotation of the Stomach. The stomach develops as an enlargement of the foregut (Fig. 104). At first fusiform (fourth week) this embryonic viscus rapidly assumes the shape of the adult stomach through an elongation and enlargement of the posterior gastric wall. With this excessive growth and the formation of the fundus and greater curvature, more space is

required than is provided in the midline of the body and it becomes necessary that the stomach rotate in some direction. The presence of the enormous embryonic liver to the right

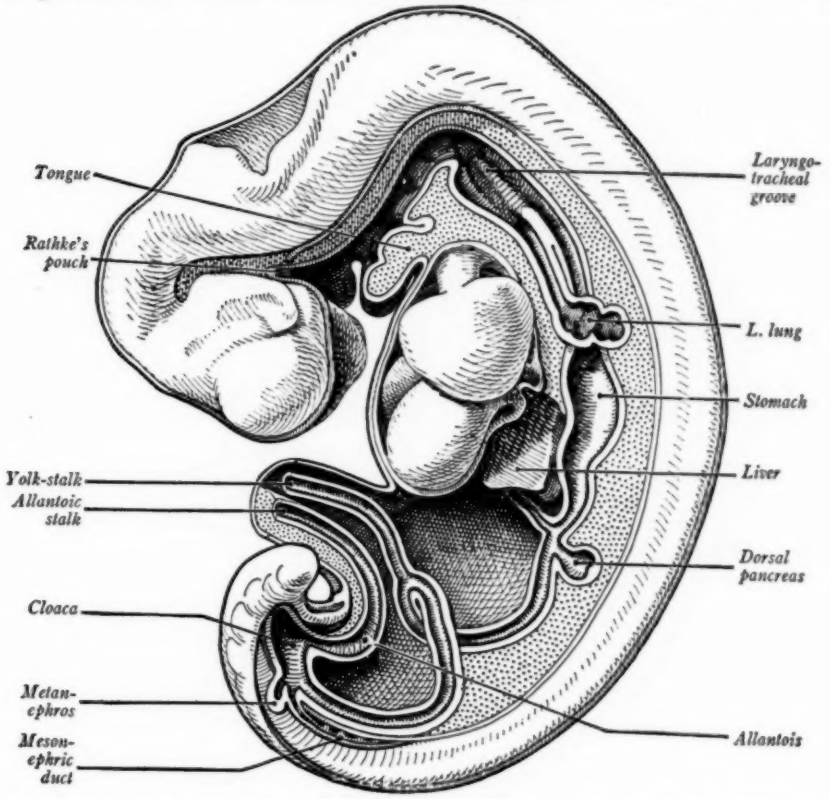

FIG. 104.—Origin of stomach from foregut. The entire enteric canal with all its derivatives and its early anatomical relationships is shown. (From His.)

causes the largest part of the stomach (fundus) to pass to the opposite side of the abdomen (fundus to the left) and as a result the lesser curvature and smaller end of the stomach (pylorus) come to be lodged beneath the liver (Fig. 104). By this rotation of 90° in which the stomach assumes its position transversely within the upper abdomen the original right side of the stomach comes to face posteriorly while the original left side faces the front. Thus is explained the apparent asymmetry of the vagus nerves with the distribution of the left vagus to the front of the stomach and the right vagus to the posterior gastric wall.

Distribution of the Left Vagus to Anterior Gastric Wall

b. Position of Duodenum. As the pylorus moves toward the right it carries with it the attached portion of small bowel. But since the dorsal mesentery is fixed to the midline this proximal bit of small intestine (duodenum) is thrown into a loop which passes first to the right, then downward, then back to the left: And this explains the formation of its three anatomical divisions. In the adult the first portion measures 2 in. and passes backward almost horizontally toward the upper end of the right kidney; the second part, 3 in. in length, descends vertically in front of the inner border of the kidney to the level of the third lumbar vertebra, and is crossed at about its middle by the root of the transverse mesocolon; the third portion, 5 in. in length, crosses from right to left in front of the third lumbar vertebra and then ascends for a short distance on the surface of the left psoas muscle to end at the duodenojejunal junction. These 3 divisions are termed, respectively the horizontal, the descending and the ascending portions (Fig. 105). From the surgical point of view a more practical division of the duodenum is that determined by the passage over this structure of the root of the transverse mesocolon which, in bisecting the loop, creates a supracolic half (to be examined from above) and an infracolic half (to be seen only after lifting the transverse colon and mesocolon). (See Fig. 107.)

Divisions of Duodenum

The portion of duodenum immediately adjacent to the pylorus is known as the bulbus duodeni, duodenal vestibule or cap. Approximately 80 per cent of duodenal ulcers occur within this "bishop's" cap.[140] The content of the duodenum is normally alkaline in reaction, due to the bile and pancreatic juice, but the bulbus duodeni, because of its location, is directly exposed to the acid gastric contents. Hence these ulcers are termed "peptic." The most frequent site for such ulcers is on the ventral wall of the duodenum and within 2 to 3 cm. of the pyloric ring. It has been pointed out that of all diagnostic data which points to peptic ulcer, the foremost evidence is the one symptom, pain (see p. 260) and that a

The Duodenal Cap

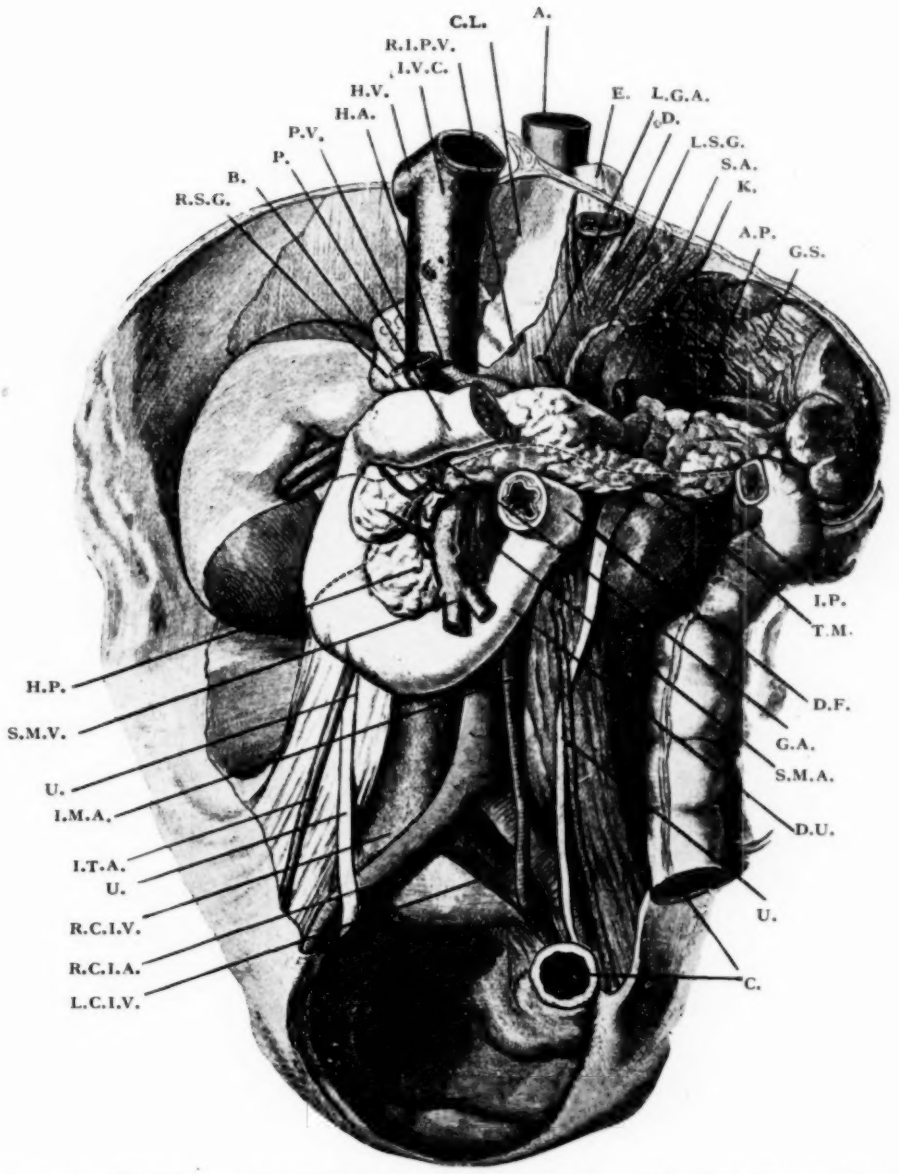

FIG. 105.—Divisions and ultimate relationships of duodenum (stomach, liver, and most of intestines have been removed). (From Cunningham.)

A., aorta; C.L., fossa for caudate lobe; R. I.P.V., right inferior phrenic vessels; I.V.C., inferior vena cava; H.V., hepatic vein; h. a., hepatic artery; P.V., portal vein; P., pylorus; B., bile-duct; R.S.G., right suprarenal gland; E., esophagus; L.G.A., left gastric artery; D., diaphragm; L. S.G., left suprarenal gland; S.A., splenic artery; K., kidney; A.P., anterior surface of pancreas; G.S., gastric surface of spleen; H.P., head of pancreas; S.M.V., superior mesenteric vein; U., ureter; I.M.A., inferior mesenteric artery; I.T. V., internal testicular vein; R.C.I.V., right common iliac vein; R.C.I.A., right common iliac artery; L.C.I.V., left common iliac vein; I.P., inferior surface of pancreas; T.M., attachment of transverse mesocolon; D.F., duodenojejunal flexure; G.A., gastroduodenal artery and neck of pancreas; S.M.A., superior mesenteric artery; DU., duodenum; C., colon.

typically cyclic or regular discomfort with relation to the intake of food constitutes presumptive evidence of ulcer. But next in order of diagnostic value comes the finding upon radiographic examination of persistent deformity of the duodenal cap.[141]

Radiographic Findings with Duodenal Ulcers

This duodenal cap is normally the only portion of the duodenum plainly seen upon the radiographic film (Fig. 106). This is true partly because the opaque medium is greatly diluted by the large quantity of duodenal digestive secretions and partly because the entire remaining length of duodenum is very rapidly traversed by the food (twenty-five to sixty seconds) so that the walls of the second and third portions are but poorly visualized.[142] The first portion of duodenum presents a shadow which is somewhat triangular in shape; its base is directed toward the pylorus and its walls are normally quite smooth (duodenal cap). A thin line (barium stream) may connect the cap and stomach shadows, providing the pylorus is open (Fig. 106). The duodenal shadow is studied as to location, size (dilated; constricted), shape (regular; irregular), and rate of filling or emptying (rapid; slow). The findings upon *x*-ray examination when a duodenal ulcer is present, are: (1) Persistent deformity in outline in the duodenal cap; (2) changes in duodenal motility; (3) secondary changes in gastric peristalsis (gastric hypermotility is an almost invariable accompaniment of duodenal ulcer); (4) niche formation. Cap deformities with ulcers are constant; deformities due to simple muscle spasms vary upon different examinations. The persistent deformity most typical of duodenal ulcers is of a coral shape. Accompanying Figures show the characteristic association of gastric hypermotility, coral shadow, and an incompetent valve with its thin barium stream joining duodenal cap-shadow with the gastric shadow. It has been stated that in competent hands radiographic study should demonstrate 90 per cent of ulcers,[143] and that roentgenographic examination alone is more accurate than all other diagnostic methods combined. The presence of either typical history (characteristic pain) or typical

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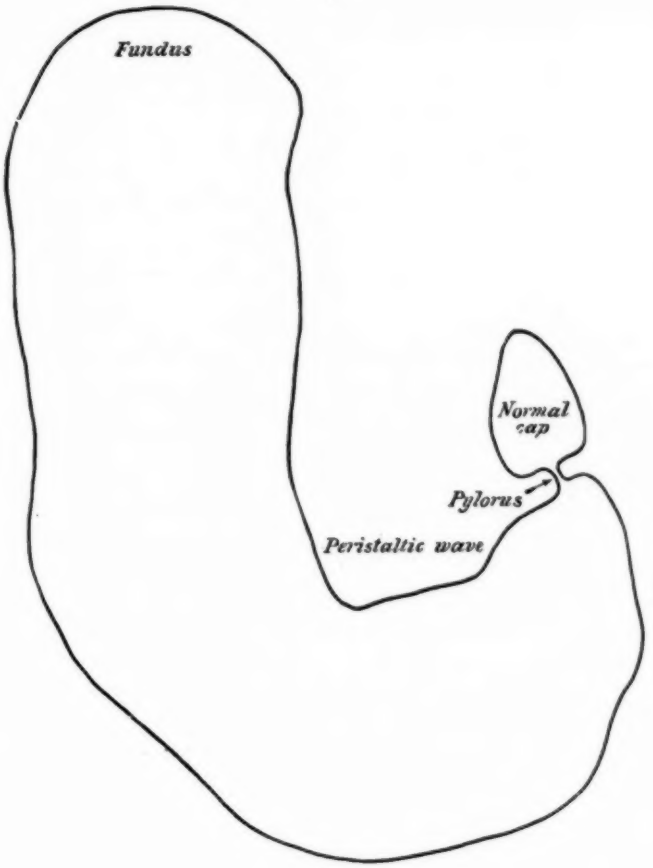
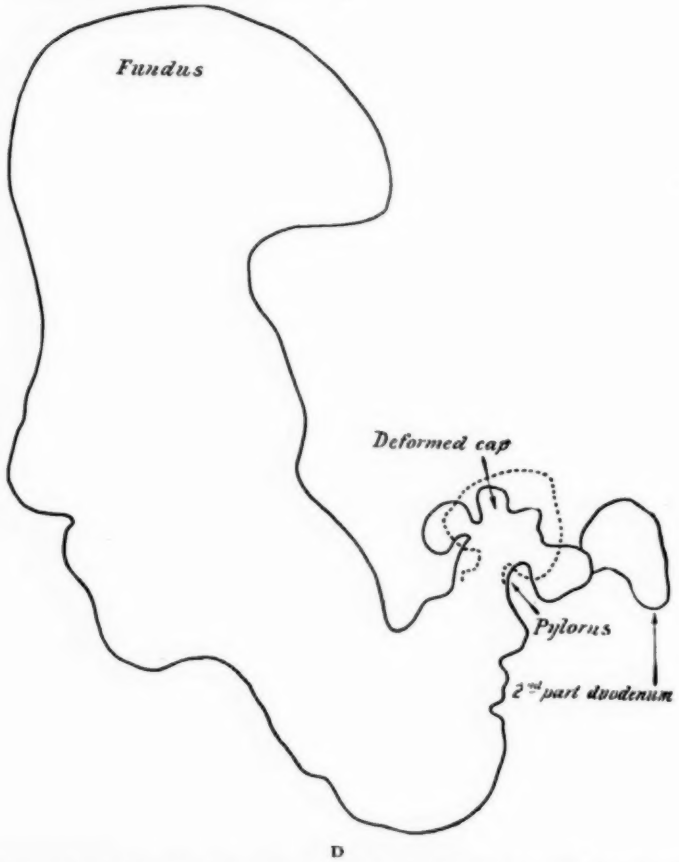


B

FIG. 106 A and B. Roentgenogram and tracing of normal duodenal cap. Note shape of stomach and duodenal cap, also barium stream representing the patent pylorus. (From Holmes and Ruggles, Roentgen Interpretation, Lea and Febigar.)

C



D

FIG. 106 C and D. Changes in stomach and duodenum caused by duodenal ulcer. Note hyperperistalsis of stomach and typical "coral" shaped deformity of duodenal cap. (From Holmes and Ruggles, Roentgen Interpretation, Lea and Febiger.)

x-ray findings furnishes presumptive evidence of ulcer, but the association of the two may be considered diagnostic.

Correlation of Data

Radiographic evidence, as is true of any single finding, is not infallible. Adhesions between duodenum and other structures, (for example the gall bladder), and pressures upon the duodenal cap from without, (tumors) are conditions which cause such mimicry as to the shadows produced that both radiographer and clinician must be constantly upon the alert. Adhesions around the duodenum, it is true, produce irregularities which are relatively slight and which tend to change with changes in the position of the patient or in the lines of traction upon the duodenum; periduodenal adhesions also cause a quite characteristic fixation of the cap which is absent with uncomplicated ulcers. Yet these differential points are not always well marked and the *x*-ray evidence may not be relied upon implicitly.[144] The deformities of cap caused by pressures from without are in the nature of smooth indentations rather than coral-shaped distortions. But there remain sufficient doubt and a sufficient percentage of errors to warrant care and conservatism in the interpretation of roentgenograms. It is probably true that actual duodenal ulcers are less frequently missed by radiographic examinations than are supposed ulcers found which can not be proved by subsequent operation or autopsy.

Limitations of Radiographic Study

Persistent Deformity of the Cap

A notable cause for diagnostic errors from radiographic examinations for duodenal ulcers is the persistence of scars and deformities after previously existing ulcers have healed. The ulcer scar, as a scar anywhere in the body, tends to be permanent. Given then, a patient who has once had a deep duodenal ulceration, subsequent study by means of *x*-rays will often reveal a persistent deformity of the cap. Because of this fact, with these patients gastrointestinal symptoms due to other lesions are liable to misinterpretation and an ulcer may be considered active as judged by the radiographic film, when in reality it is quiescent or healed. The statement bears repetition that all diagnostic data must be correlated if errors are to be avoided.

Surgical Significance of Duodenojejunal Junction

c. The formation of the duodenojejunal junction. The point of union of duodenum with jejunum is of considerable importance as an intra-abdominal landmark. From this point measurements are taken for the site of the opening in the jejunum for simple jejunostomy, for gastroenterostomy or for cholecystenterostomy made by the retrocolic route of anastomosis. The junction also marks the uppermost point of origin of the adult mesentery (the jejunoileal mesentery) and at this point the following three peritoneal reflections meet, the under surface of the transverse mesocolon, the upper extremity of the right leaf of the mesentery, and the posterior parietal peritoneal reflection as it covers the terminal duodenum. The junction of duodenum and jejunum is synonymously termed the duodenojejunal angle. The angulation is caused by the fact that the terminal (third or ascending) portion of the duodenum is directed backward and slightly upward while proximal jejunum passes downward and to the left (Fig. 107).

Locating the Proximal Jejunum

The duodenojejunal junction lies slightly to the left of the second lumbar vertebra; it is at this point that the jejunum appears to suddenly enter the peritoneal cavity from below the transverse mesocolon (Fig. 108). The reason for this abrupt entrance of the jejunum into the greater peritoneal cavity will be explained with the study of the rotation of the small intestine). The proximal portion of the jejunum is located by drawing the transverse colon strongly upward, then passing the index finger along the under surface of the root of the transverse mesocolon; the desired segment is hooked up at the point where the bowel pierces the mesocolon just to the left of the spinal column to enter the infracolic division of the general peritoneal cavity. During these maneuvers the forefinger enters a small recess located just to the left of the second lumbar vertebra immediately below the inferior surface of the body of the pancreas. The superior mesenteric vessels are palpable to the right of this point of origin of the jejunum; they mark the upper extremity of the mesentery of the small bowel. The first part of the jejunum always

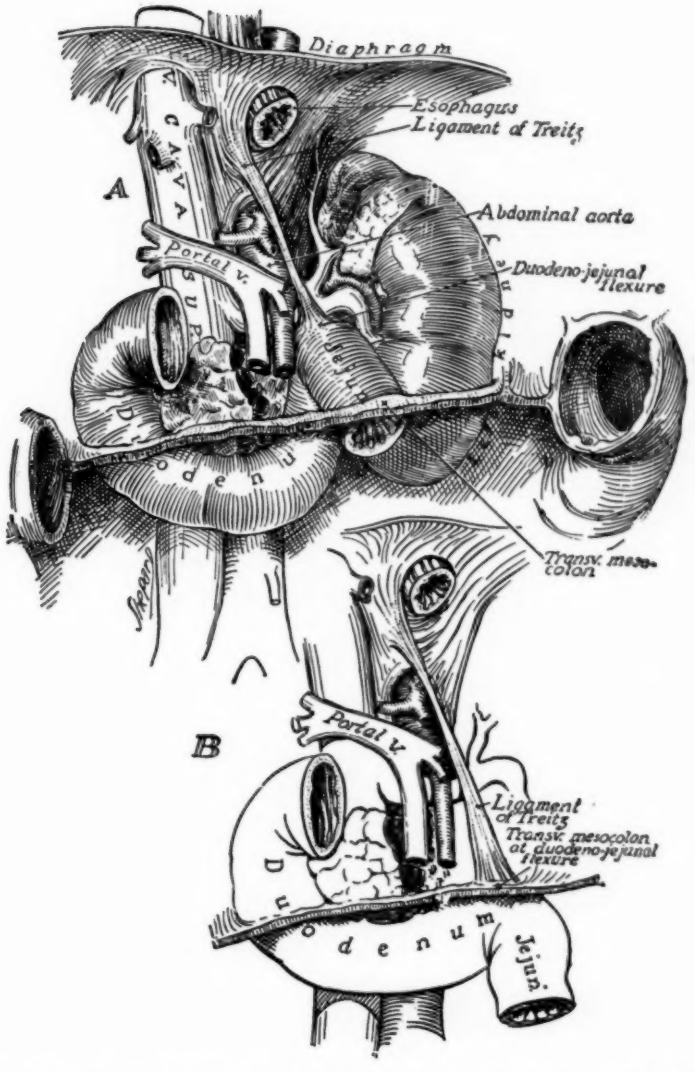


FIG. 107. The duodenojejunal junction or angle. Schematic representation of duodenum and its retroperitoneal relationships. Variations in the angle as described by Roeder.

A. The U-type of duodenum with the ligament of Treitz elevating the duodenojejunal flexure above the transverse mesocolon.

B. The C-type of duodenum with the ligament of Treitz of greater length, allowing the flexure to lie just below the transverse mesocolon. Compare the angulation of the two flexures.

passes downward and slightly to the left from its point of attachment at the duodenojejunal angle. This is the only segment of small intestine the location and direction of which

FIG. 108. The jejunum appears within the infracolic division of the peritoneal cavity, springing from beneath the root of the transverse mesocolon.

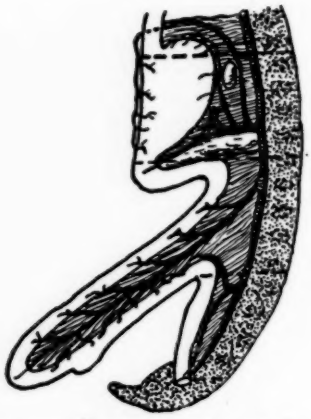


FIG. 109. Review of the parts of the enteric canal at the period marked by presence of primary or umbilical bowel loop. Note position of cecum; arrangement of vessels and of developing glands within the dorsal mesentery.

are constant.[145] The ligament of Treitz proves of service in locating the proximal jejunum by means of simple inspection. This is a fibromuscular band which originates from the right crus of the diaphragm and the tissue about the celiac axis and passes to the duodenojejunal junction; it is often referred to as the suspensory ligament of the duodenum. When the transverse mesocolon is put upon an upward stretch the course of this ligament is visible; the structure in addition may be palpated as it leads, as a guide, to the beginning of the jejunum.

The Ligament of Treitz

When any doubt remains that the proximal jejunum has been correctly located the following test will settle the matter: pull downward upon the loop in question; if it is found to be fixed, the loop is most certainly the proximal jejunum; but if it is not fixed, and traction results in the delivery of a long portion of bowel, it is obvious that the loop in hand is not located immediately below the fixed duodenojejunal junction and is not proximal jejunum.

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d. Rotation of Intestines. The intestines rotate during development upon the superior mesenteric artery as an axis. To understand this phenomenon it is necessary to revert to a study of the primary loop of the primitive bowel (six to ten week embryos) and to visualize the arrangement of the enteric tract at this period (Fig. 109). The primary loop, it will be recalled, consists of a descending limb from which all of jejunum and most of ileum arise; of an ascending limb from which develop the remainder of ileum, and beyond the cecal bud, the cecum, appendix, ascending colon and a large part of the transverse colon; of a vitellointestinal duct, springing from the free bowel border at the apex of the loop and passing to the yolk vesicle; and finally, of a superior mesenteric artery which traverses the entire length of the dorsal mesentery of the loop, supplying all of its derivatives. At this developmental stage the only attachment to the posterior abdominal wall of this entire length of intestines (jejunum, ileum, cecum, appendix, ascending colon, transverse colon) is found at the base of the primary enteric loop; that is, at a narrow mesenteric isthmus extending between the two limbs of the loop at their points of origin. This site of attachment is known as the duodenocolic isthmus; for at the base of the descending (proximal) limb lies developing duodenum, while at the base of the ascending (distal) limb is located the developing colon (a point near the future splenic flexure). This duodenocolic isthmus plays a rôle of the utmost importance in determining the final arrangement of the enteric tract within the abdomen and a close relationship between duodenum and colon is retained throughout life (see duodenocolic ligaments).

Importance of the Duodeno-colic Isthmus

When the yolk vesicle and vitellointestinal duct become of less importance and begin their degeneration the developing intestines are no longer pulled outward into the umbilical cord but, due to their mesenteric attachment at the duodenocolic isthmus to the posterior abdominal wall, they are drawn back into the abdominal cavity as the embryo elongates and

Reduction of Embryonic Umbilical Herniation of Bowel

the abdomen enlarges. So great has been the growth of the derivatives of the primary loop of bowel by the time of their return to the abdomen (particularly of the descending limb with its jejunoileal segments) that they can no longer remain in the midline but must, of necessity, be thrown into turns and coils some of which are oblique and others transverse to the long axis of the abdomen. The phenomenon of intestinal rotation takes place coincidentally with this spontaneous replacement of the intestines into the abdomen. Rotation takes place upon the axis of the superior mesenteric artery at the duodenocolic isthmus[146,147] and continues through an arc of 180°. During the process the ascending or distal limb of the primary intestinal loop comes to overlie the descending or proximal limb (i.e. the large bowel comes to lie on top of the small bowel) and the superior mesenteric artery itself undergoes actual torsion through the half circle (180°) with a resulting complete rearrangement of its peripheral branches (see blood-supply of gastrointestinal tract). As a result of bowel rotation the cecum and appendix are carried to the right upper quadrant to be lodged belowthe liver (Fig. 110A); the transverse colon comes to be superimposed upon the duodenum; and the terminal duodenum is carried below the superior mesenteric artery near the point of origin of this great vascular trunk. The practical significance of this latter arrangement whereby the superior mesenteric artery crosses over the terminal duodenum has already been discussed during the consideration of that important form of high intestinal obstruction variously known as gastro-mesenteric ileus, duodenomesenteric ileus, or simply as mesenteric ileus (See p. 219).

End-results of Intestinal Rotation

Fetal Position of Appendix; Appendicitis Simulating Cholecystitis

The position of the appendix at the termination of intestinal rotation (below the liver) is but temporary and a rapid growth in cecum follows which carries the appendix to its normal situation in the right lower quadrant. With this descent of the cecum the ascending colon becomes differentiated (Fig. 110B). The right colic flexure (hepatic flexure) of the colon

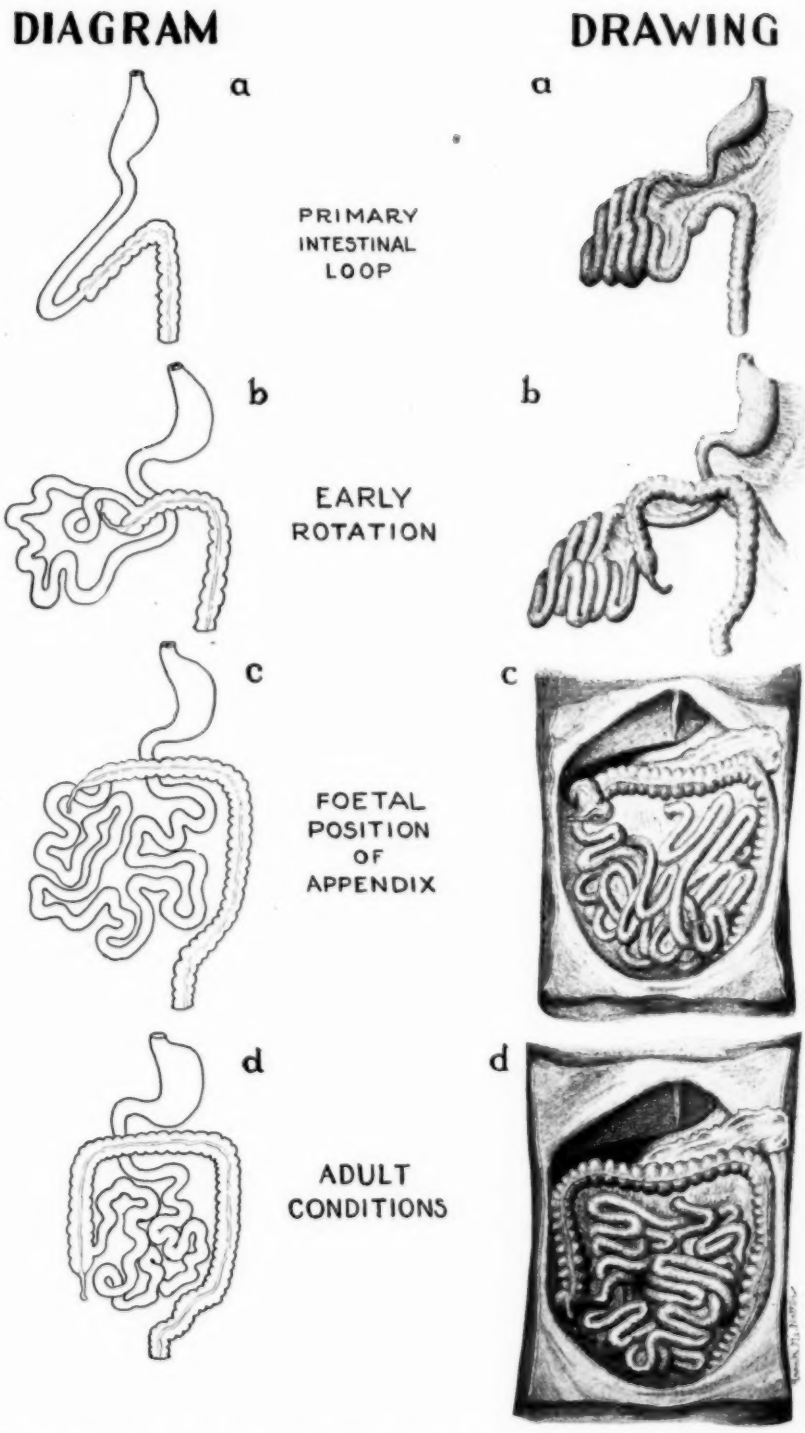

FIG. 110. Changes in enteric canal from period of the primary intestinal loop to establishment of adult conditions. (Redrawn after Huntington.)

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will be studied more in detail as the liver and gall bladder are subsequently dealt with. Due to faulty development the appendix and cecum, at times, remain in the high or embryonic position. This occurs in about 2 per cent of individuals. In such instances when the veriform appendix becomes acutely inflamed, the signs and symptoms produced are referable to the upper rather than to the lower abdomen and some disorder of the gall bladder or biliary ducts may be closely simulated.

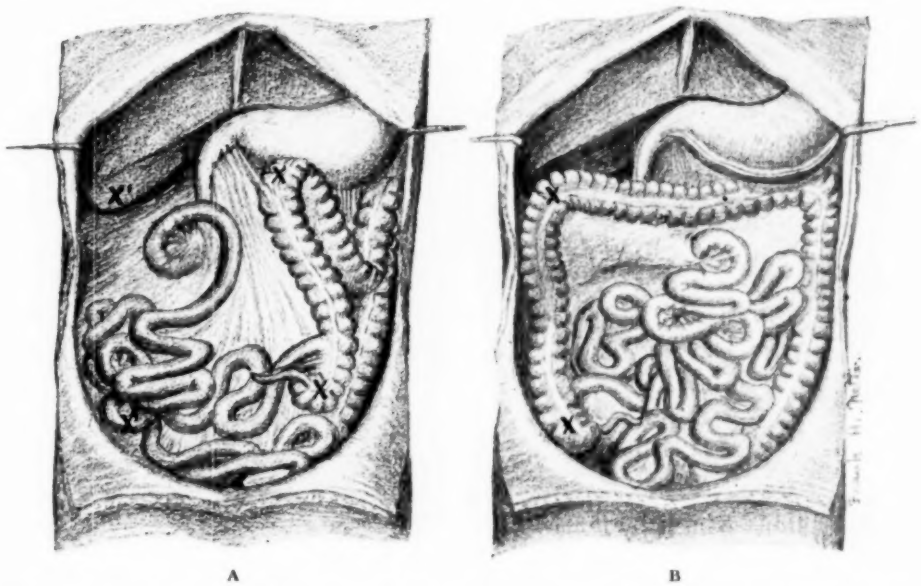
A Model for the Study of Intestinal Rotation

For further study of intestinal rotation reference must be made to special textbooks on embryology or gastroenterology. Both written descriptions and diagrams prove unsatisfactory for clarifying the phenomenon of rotation. The two chief reasons for this difficulty are, first, that three dimensions must be dealt with and second, that during or after rotation certain parts of bowel hide or obscure other parts. It has been pointed out that the alimentary canal of the cat furnishes an excellent model for use in studying the rotation of the intestines and gives a convenient macroscopic illustration of conditions which in humans exist only during early embryonic life.[148] No rotation of the intestines occurs in the cat. Hence the student finds in this animal a simple arrangement of the bowels and by picking up the cat's cecum and placing it below the liver he at once may see the results that would be produced by rotation, and he may then study the secondary changes which are dependent upon the fact that large bowel has been superimposed upon small bowel. Huntington has described a technic for dissecting and thus studying the intestinal canal of a cat and points out that if the main abdominal vessels be injected with liquid plaster-of-Paris a specimen is created which is of particular value for demonstration and which may be kept indefinitely, preserving the entire preparation in a 50 per cent solution of alcohol.

In rare instances an adult human is encountered in whom no rotation of intestines has occurred (Fig. 111A). Here all coils of small intestine lie largely within the midline or right

side of the abdomen while all the large intestine lies to the left side. Hence the abdominal cavity is not divided into supracolic and infracolic divisions; the duodenum, as might be expected in such circumstances, is plainly visible throughout its entire course and is nowhere retroperitoneal; all portions of enteric canal retain mesenteries, including duodenum,

Non-rotation of the Bowel in Man



A B

FIG. 111. Study of establishment of final arrangement of gastrointestinal tract within the abdomen.

A. Rare case of non-rotation of intestines in human (redrawn from Huntington).

B. Conditions after rotation has occurred. To place points X and X on points X′ and X′ of Figure 111A will immediately explain all of the secondary changes pictured in Figure 111B.

ascending colon, descending colon and colic flexures. Pictures of such cases of non-rotation prove valuable for purposes of study. With such a picture it is possible to imagine picking up the cecum and placing it below the liver (imitating intestinal rotation as it would normally occur; see Fig. 111B where point x is superimposed on point x′). Secondary changes incident to bowel rotation immediately appear: the duodenum is pushed backward against the posterior abdominal wall by the transverse colon and the duodenum is in part obscured

from view; the proximal jejunum appears to pop out from below the transverse mesocolon as it suddenly enters the greater peritoneal cavity; the small intestine appears clumped in the central regions of the abdomen; while the large bowel describes a huge loop traversing the periphery of the abdominal cavity. This final arrangement of small and large intestines makes clear why with small bowel obstructions the center of the abdomen tends to become distended and why typical "ladder patterns" may appear, with midline loops of distended bowel visible externally, one above the other, like the rounds or rungs of a ladder; and explains, also, why with large bowel obstructions, particularly when of sigmoid colon, there may be noted marked distention in the flanks or abdominal circumference associated with a relatively flat or nondistended central region.

Visible Distentions of Obstructed Bowel

4. *Final Attachments of the Gastrointestinal Tract.* Preceding embryological studies (Origin of the Peritoneal Cavity; Origin of the Gastrointestinal Tract; Distribution Within the Abdomen of the Enteric Canal) furnish a sound basis for a clear comprehension of the manner in which the investing serous membrane ultimately connects the various portions of the alimentary canal and its digestive glands to one another and to the abdominal parieties. These final attachments of the enteric tract prove most complex and difficult thoroughly to understand when dealt with through any other mode of approach.

The gastrointestinal tract always remains basically a midline structure. That there are distinct practical advantages for the surgeon in keeping this viewpoint in mind will be amply illustrated as reliable methods for mobilizing individual anatomical units of the tract are considered and as other technical and diagnostic measures are taken up. Originally a simple straight tube, suspended in the midline by an uncomplicated peritoneal reflection or mesentery, the enteric canal adheres fundamentally to this early arrangement and late developmental changes (final peritoneal attachments) are in

reality superficial in significance as contrasted with the essential design or pattern which is determined in early embryonic life (see vascular, and nerve supply of bowel).

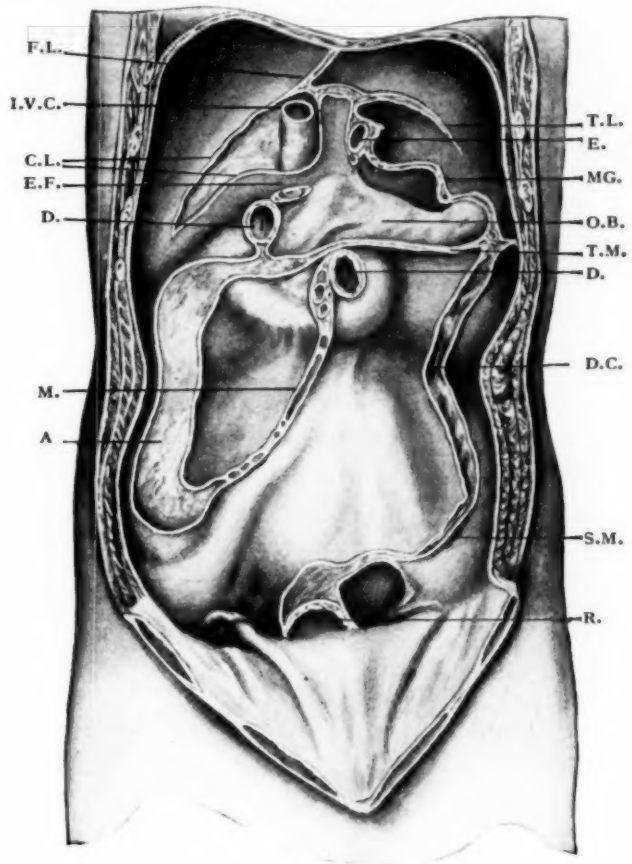


FIG. 112. Empty cavity.

The abdominal organs have been removed, exposing the "raw" or "uncovered" areas of the posterior wall (zones devoid of peritoneum). (After Morris' Anatomy, from McMurrich's Development of the Human Body, Blakiston.)

F.L., falciform ligament. I.V.C., inferior vena cava. C.L., coronary ligament. E.F., epiploic foramen. D, duodenum. M, mesentery of small intestine. A, area of attachment of ascending colon. R, rectum. S.M., sigmoid mesocolon. D.C., area of attachment of descending colon. T.M., transverse mesocolon. O.B., omental bursa. MG., mesogastrium. E, esophagus. T.L., left triangular ligament.

Under the heading of "Raw" or "Uncovered" Areas of the Abdomen illustrations have been inserted to show exactly the lines of fixation of stomach, intestines and digestive glands, to the abdominal walls (Fig. 112). These sites of attach-

ment will now be minutely studied, together with practical points which bear directly upon such details concerning gastrointestinal fixation and support.

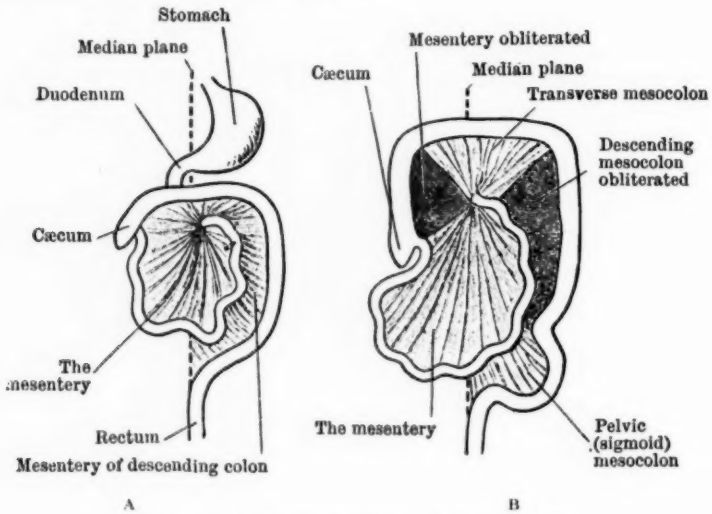


FIG. 113. Ultimate fixations of large bowel.

A. Entire intestinal tract (large and small bowel) supplied with a dorsal mesentery.
B. Later stage, showing (shaded areas) portions of large intestine which become fixed or partially retroperitoneal. (From Cunningham.)

a. Attachments of the Colon. Those portions of colon brought into direct contact with the parietal peritoneum (abdominal walls) during the process of intestinal rotation lose their primitive mesenteries and become fixed or partially retroperitoneal; but the portions of colon which at the termination of bowel rotation are *not* in direct contact with abdominal wall but overlie other intra-abdominal structures, retain mesenteries. Thus the transverse colon, which overlies duodenum, is permanently supplied by a transverse mesocolon, and the pelvic colon (sigmoid) which on account of its extreme length is too voluminous to lie smoothly in contact with pelvic peritoneum but necessarily overlies other structures, is always supplied by a mesocolon (pelvic or sigmoid mesocolon; see volvulus). All portions of colon aside from these transverse and pelvic divisions are, as a rule, relatively fixed (Fig. 113). The line of peritoneal reflexion from the ascending

and descending colons onto the posterior abdominal wall runs vertically upward from the centers of the iliac crests. The right colic flexure (hepatic) is fixed at the level of the first lumbar spine; the left colic flexure (splenic) reaches to the level of the twelfth thoracic spine, or the tenth rib posteriorly (this is the heighest point reached by any part of the colon and lies about 5 in. above the level of the left iliac crest). Viewed from behind the large intestine on both sides overlaps the lateral borders of the kidneys and lies parallel to the lateral border of the sacrospinalis muscle. The transverse mesocolon has been extensively studied elsewhere (abdominal watersheds p. 141); and it was pointed out that this great transverse barrier separates the peritoneal cavity into two major divisions, supracolic and infracolic; that its root bisects the loop of the duodenum; that it has a slight obliquity upward from right to left; that this structure aids in forming the floor of the omental bursa or lesser peritoneal cavity, and other details of practical moment were discussed (Fig. 113).

The arrangement of the colic attachments, then, as usually found by the operator is as follows: more or less completely fixed are cecum, ascending colon, right (hepatic) flexure, left (splenic) flexure, descending colon, iliac colon, (and rectum); uniformly supplied with mesenteries are transverse colon and pelvic colon. At times the colic fusions with parietal wall do not continue to completion and quite commonly one encounters a mesocecum (cecum mobile), and some degree of ascending mesocolon will be found in 26 per cent of adults while some form of descending mesocolon may be expected in 36 per cent of cases.[149]

The Re-Creation of Mesentereis

When mobilizing the ascending colon as for the removal of a growth (neoplasm; ileocecal tuberculosis) the attack upon the colon is best begun from the lateral rather than from the median border.[150] When the parietal peritoneum has been incised to the right of the ascending colon, this structure may be lifted from its bed by dry or blunt dissection, re-creating, in a sense, an ascending mesocolon or dorsal mesentery with

its midline attachment, and the vessels may be cut, clamped and ligated, secundum artem, under full vision and safe control (Fig. 114). By this method the ureter is safeguarded

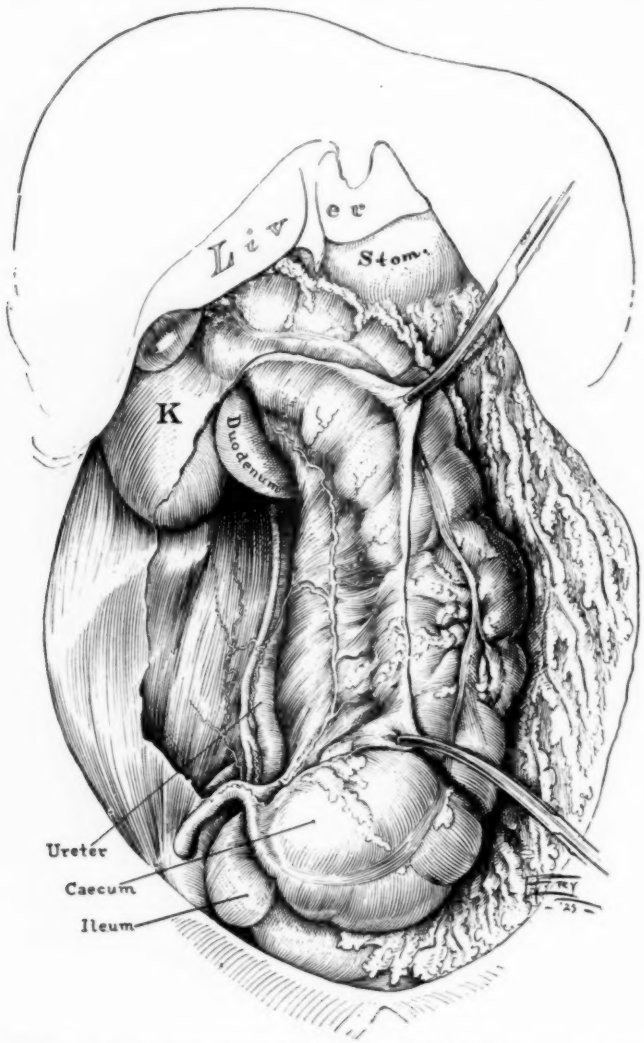


FIG. 114. Division of parietal peritoneum with mobilization of cecum and colon. (Rankin and Scholl).

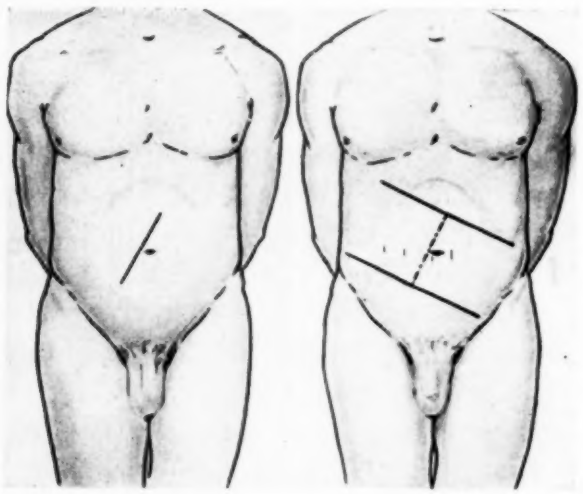
as well. In a similar fashion the descending colon is best mobilized by working toward the midline from the lateral margin of the bowel. So relatively easy and safe is this approach that to any who have employed it the wisdom of regarding the

gastrointestinal tract as still basically a midline structure must be obvious.

b. Attachment of Small Intestine. Except for the duodenum the entire small intestine (20 ft.) is attached to the abdominal wall along a straight line but 6 in. in length. The intestinal loops coil and twist freely throughout the abdomen, suspended from the posterior wall by a lamina of connective tissue covered on each side by peritoneum (the jejunoileal mesentery or mesentery proper). The root of the mesentery follows an oblique line from the duodenojejunal junction (left side of second lumbar vertebra) to the right iliac fossa. In its oblique course it overlies the aorta, inferior vena cava, right ureter, and right psoas major muscle (see Fig. 112). The word mesentery (Gr. *mesos*, middle + *enteron*, intestine) properly signifies that this great encircling fold or double layer of peritoneum supplies small bowel only. The mesentery is not in reality fan-shaped as it is often described, for although the long free border is enormously frilled out the indentations and waves do not reach to the mesenteric root which is quite smooth. To construct a model of the structure, using non-organic materials to obtain the proportionate inequality between free-and root-borders would indeed tax the ingenuity. Winslow aptly compared the mesentery to a chamois, one border of which had been teased or thinned out while the other retained its full thickness; the one margin being flat, the other irregular, waved and elongated.[151]

The direction, course, length and arrangement of this final attachment of small intestine are determined quite largely by the superior mesenteric artery which in the adult is found to traverse the mesenteric root. It will be recalled that during intestinal rotation the only attachment of small bowel to parietes is located at the duodenocolic isthmus and that rotation takes place about the superior mesenteric artery as an axis, large intestine coming to overlie small intestine. As the ascending colon and cecum subsequently become fixed, by adhering to the mesoderm of the developing posterior

abdominal wall, so also does the superior mesenteric artery becomes attached to those structures which it overlies (aorta, right ureter, vena cava, right psoas major muscle); hence the



A B

FIG. 115.

A. Showing approximately the line of the mesenteric root as traced on the abdominal wall.

B. Two oblique lines (black) drawn at right angles to the two ends of line (dotted) of the mesenteric root. The upper, middle and lower compartments, here indicated, contain in most instances the upper, middle, and lower thirds of the small intestine respectively. (From Monks.)

small bowel (jejunum and ileum) receives its new and final attachment to the parietes along the oblique line described by and representing the course of the artery. (See Fig. 112; repeat process with models; see p. 298.)

Replacement of Intestinal Loops after Operations

The course taken by the mesenterium or mesentery as mapped out upon the anterior surface of the abdominal wall is shown in Figure 115. A study of the attachment of the bowel makes it clear that although individual loops are free to move from side to side and for a limited range also upward and downward, yet they necessarily adhere to a relatively constant general position. And it has been repeatedly shown through tagging or marking individual loops that even though these be mechanically displaced or pushed about they will soon

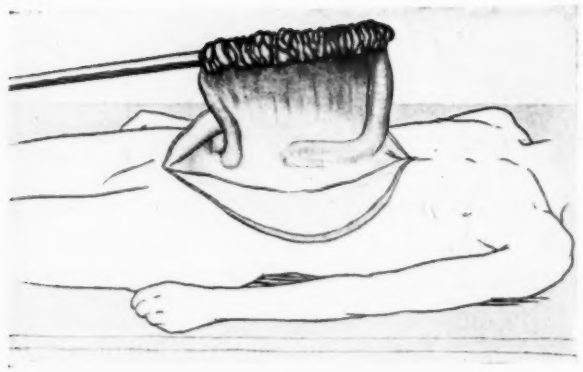
spontaneously rearrange themselves within the abdomen. Thus the surgeon need not attempt to replace the intestinal loops to their normal positions (a task which might prove puzzling or even impossible) after he has moved them about during an abdominal operation. It is asserted that only rarely will a loop of the lowest point of the small bowel be encountered high in the abdomen or a high loop be found near the pubis or pelvis. The only loop in which both position and direction are absolutely constant however is the proximal jejunum, which passes downward and to the left from the duodendojejunal juncture to the left of the second lumbar vertebra.

The Three Topographical Intestinal Zones

Both diagnostician and operator are greatly aided by knowledge as to what part of the bowel is most likely to lie beneath a given site on the body surface. Monks states[152] that "in a general way it may be said the uppermost third of the intestine usually occupies the large cavity on the left side of the abdomen, high up under the ribs; the middle third occupies the middle third of the abdomen and the left iliac fossa; and the lowest third helps to fill the pelvis and right iliac fossa." To mark upon the body wall these three areas or bowel zones, two oblique lines are drawn at right angles to the two ends of the mesenteric root as this is traced upon the anterior abdominal wall.

Methods for Study of the Mesentery

Monks suggests an excellent method in which to study the connections between intestine and posterior abdominal wall. This is as follows: Make a small hole in the ileum a few inches proximal to the ileocecal valve; push a stout glass rod about a foot in length into the intestinal lumen through this small hole; gradually thread the glass rod through the intestinal loop (i.e., gather the intestines together upon this rod); then it will be found that without undue force the entire 21 ft. of small intestine may be readily gathered together over the rod, forming a linear mass about 1 ft., in length; now place the rod with its intestinal contents in the line of the mesenteric root and the mesentery may be studied at will (Fig. 116A).



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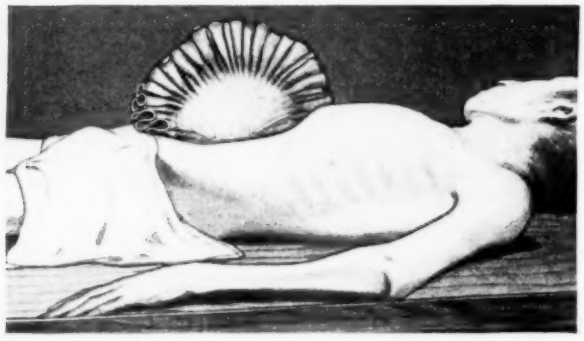

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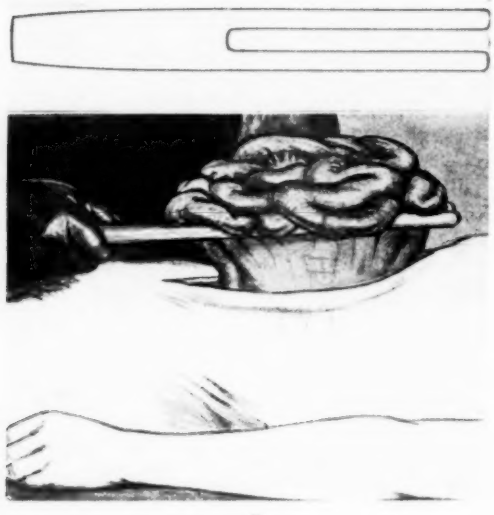


C

FIG. 116.

A. The small intestine is puckered upon a rod. It is surprising with what ease this can be accomplished. The rod cannot be pushed into the bowel, but the bowel can be drawn, loop by loop, over the end of the rod and "puckered" upon it, so that the various loops become packed together. In some later experiments occasionally a tube was used instead of a rod. (Drawn from a photograph.)

B. The intestinal tube has been thrown into alternate curves which are held in place by means of a stout copper wire within the gut. The alternating arrangement of the loops is most evident near the lower end of the ileum. The mesentery is a flapup to the place where the ruffled edge begins. (Drawn with slight modifications, from a photograph.)

C. The elevation of all the coils of the small intestine upon an instrument especially designed for this purpose.

(From Monks, *Surg. Gynec. Obst.*)

A practical advantage from being thus able to pass a short rod throughout loop after loop of small bowel immediately suggests itself. In acute intestinal obstruction when the intes-

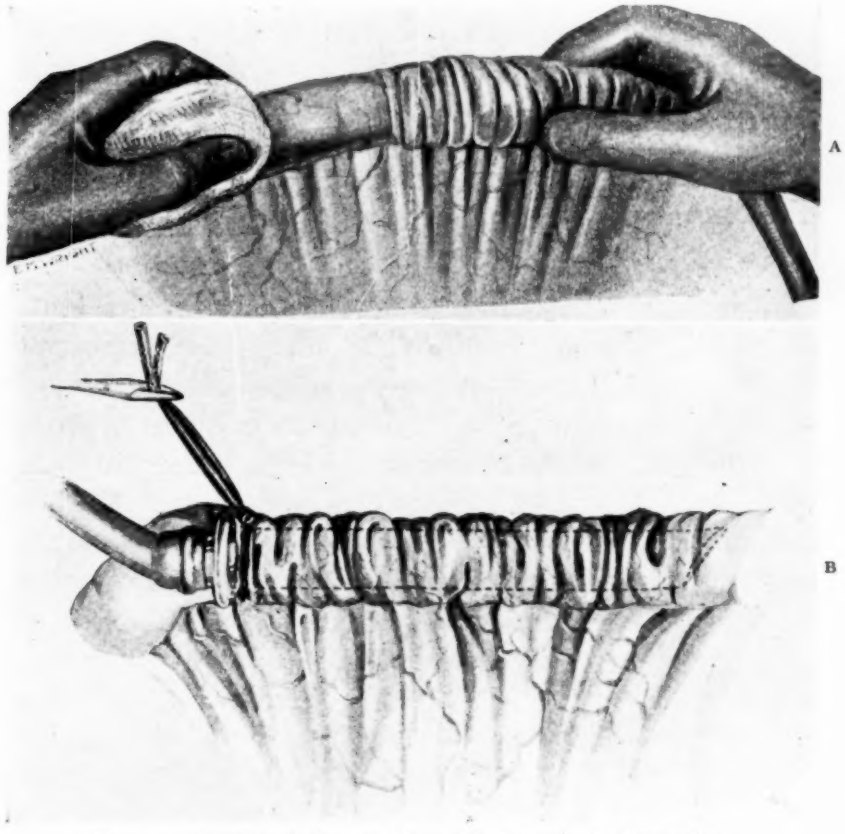


FIG. 117. Suction drainage of bowel in intestinal obstruction.

A. Bowel being pushed gently along tube.

B. Position of tube when as much of the gut as possible has been drained by it.

(From Moynihan's Abdominal Operations, Saunders.)

Draining the Bowel in Acute Intestinal Obstruction

tine cephalad to the obstruction is greatly distended with highly toxic material or when the ballooning of the bowel is so great as to interfere materially with the necessary exploration it is possible to drain many individual loops by introducing a suction device into the intestinal lumen through a single small opening. It is found that in operating 6 to 8 or more feet of bowel can easily be reached by a tube 6 inches in length (Fig. 117). It is important that the bowel be threaded onto the rod

rather than an attempt made to force the rod into the bowel.[153] Gentleness is obviously requisite. The maneuver is facilitated by holding the gut, as it is being coaxed onto the suction tube, by means of a piece of moist gauze. When as much intestine has been carried onto the tube as is convenient, additional loops may be emptied as the assistant gently milks the distended coils in the direction of the sucker. If the opening thus made in bowel is carefully repaired with through-and-through (locked; Connell) and seroserous (Lembert; Cushing) sutures the slight peritoneal contamination which may occur need not be particularly dreaded for the peritoneum is very resistant against colon bacilli unless the contamination be continuous or overwhelming. The maneuver (enterotomy) facilitates the exploration tremendously and the wisdom in draining the bowel of its toxic contents in acute obstruction is well established; this drainage is, in fact, almost an essential feature of such an operation; the measure has been repeatedly employed with impunity and often proves life-saving. The statement has previously been made that "no operation for acute intestinal obstruction can be considered complete which leaves an intestine, whose function it is to absorb, overdistended by contents of an offensive and poisonous nature."

Examining the Mesenterium

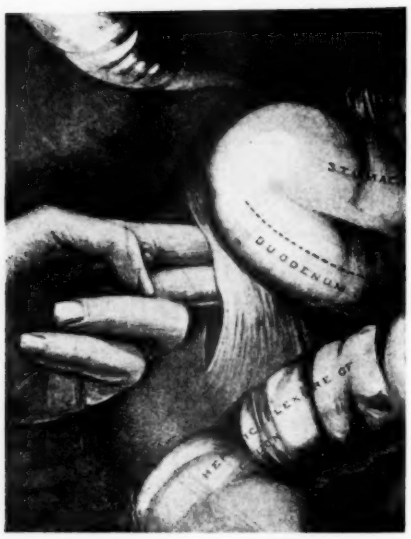
A second method suggested for studing the mesentery, (Fig. 116B) is to thread a heavy wire through the intestinal lumen, in place of using a glass rod, and by kinking the wire, first to the right then to the left, again and again, to throw the entire jejunoileum into a series of short loops which center over the line of the mesenteric root and which may be readily handled or moved from side to side in examining the mesentery. A third method (Fig. 116C) and one which does away with the necessity for opening the intestinal lumen during the study, is to apply one blade of a large (1 ft.) fork to each side of the mesenteric root, and by lifting the fork anteriorly, to gather the intestinal coils into a linear mass above the prongs, exposing the bulk of the mesentery below. By moving the clustered bowels and extremity of the mesentery toward

[153] A. J. S., n. s. Vol. IX, No. 1, p. 196

the right, one entirely exposes the left lower abdominal quadrant; while moving them to the left, one makes the right lower quadrant, ready for examination. The mesentery is seen to serve as a large oblique partition separating the two abdominal fossae; it is thick and smooth at its base and consists of a series of waves or ruffles in the outer third or fourth (free border); the intestine is suspended as on a hinge.

Between the two layers of mesentery are (a), the intestine, (b) extraperitoneal fat, areolar and fibrous tissue and a few smooth muscle fibers, (c) the mesenteric lymph glands (40 to 150 in number), (d) the mesenteric nerve plexuses and lymph vessels, (e) the jejunal and ileal branches of the superior mesenteric vessels. Embryologically considered the real root of the mesentery is the duodenocolic isthmus or that point where the vessels enter (see rotation and development of bowel). The thickness and opacity of the mesentery vary and as a rule the structure is more translucent at its upper end while the fat and consequent opacity increase markedly as the lower end is approached. This observation has some value for the surgeon as it aids him in orienting himself and in identifying the loops of jejunum and ileum as they are handled.

c. Attachments of the Duodenum. These have already been alluded to and may be summarized as follows: the duodenum, which was originally suspended from the median plane of the posterior abdominal wall (primitive mesoduodenum) is forced backward against the posterior wall by the transverse colon after rotation of the bowel has taken place. The duodenum, then, becomes adherent to the posterior parietes and is henceforth considered as a retroperitoneal or partially retroperitoneal structure. Reference has repeatedly been made to the duodenojejunal angle or junction of duodenum with jejunum. The attachments to the proximal duodenum of the lesser omentum (hepatoduodenal ligament) and of the right extremity of the gastrocolic ligament (see duodenocolic ligament) will be dealt with as the attachments of the stomach are reviewed.



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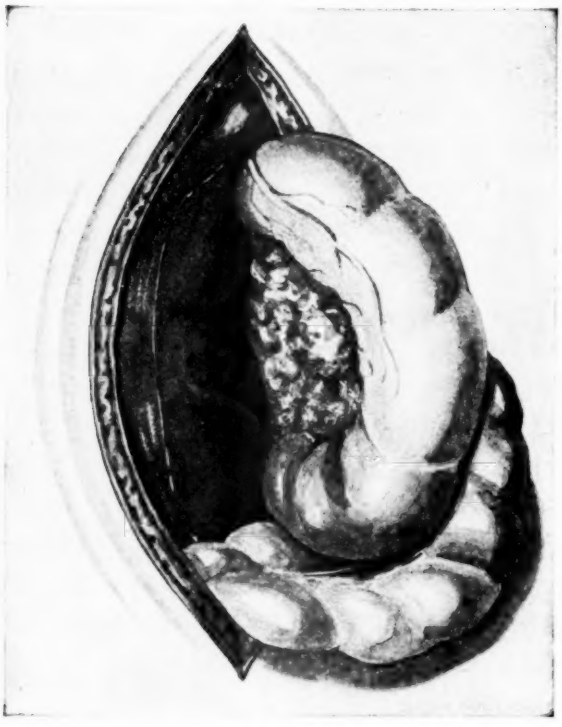

B

FIG. 118. Duodenal mobilization to expose retroperitoneal portion of common bile duct. (A from Taylor's Operative Surgery; Wood. B from Moynihan's Abdominal Operations, Saunders.)

Mobilizing the Duodenum

There are times when it is desirable or necessary to mobilize the duodenum, for example, as a preliminary measure to the performance of a gastroduodenostomy or in order to gain access to the terminal (retroduodenal) portion of the common bile duct, or the head of the pancreas.[154] Here, as elsewhere, it should be recalled that the enteric canal is basically and originally a midline derivative. The mobilization may be safely effected as follows: incise the peritoneum vertically 1 in. lateral to the descending portion of the duodenal loop, that is, over the right kidney; by blunt dissection displace the entire duodenal loop medially (toward the left), re-establishing as it were the primitive median plane attachment; make sufficient traction toward the left to expose the posterior surface of duodenum and the head of the pancreas with its contained terminal portion of the common bile duct (Fig. 118).

Exposure of Terminal Common Bile Duct

The work of the diagnostician, no less than that of the operator, as following illustrative points tend to demonstrate, is rendered both more simple and accurate through acquaintance with details concerning gastrointestinal development and final anatomical arrangements.

EPONYM

JOSEF THOMAYER (1853–1927)*

Eponym Definition: Thomayer's sign—a means of distinguishing inflammatory from non-inflammatory ascites. In inflammatory conditions of the peritoneum (malignant peritonitis, tuberculous peritonitis) the mesentery contracts, drawing the intestines over to the right side; consequently, when the patient lies on his back, tympany is elicited on the right side, dullness on the left.

CONTRIBUTION TO THE DIAGNOSIS OF TUBERCULOUS AND CARCINOMATOUS LESIONS OF THE PERITONEUM†

DR. JOSEPH THOMAYER

The clinical diagnosis of tuberculous and carcinomatous peritonitis is by some considered as difficult, by others as easy, a circumstance the obvious explanation of which is the type of cases the one or the other has for investigation. Undoubtedly the diagnosis of both named affections can be very easy. In dealing, for example, with a patient who has a palpable cancer of the stomach, when in the course of the affection distinct secondary nodules develop in the abdomen, and when in addition the abdomen begins to fill with fluid, the examining physician arrives at the correct diagnosis without necessarily being particularly clever. The same may be said of cases where besides a marked pulmonary tuberculosis a free ascites develops with severe lower abdominal pain, unassociated with disease of the liver, kidney, or heart.

Yet circumstances differ when we have before us a patient who exhibits all symptoms of marked ascites but with whom nevertheless the results of investigations regarding other organs and tissue remain negative.

We know that tuberculous peritonitis can be associated with isolated tuberculous mesenteric lymph glands or tuberculosis of the urogenital system or insignificant pulmonary involvement and marked intestinal tuberculosis; in short in a number of cases which present on the whole typical peritoneal involvement without the cause being readily diagnosed. I think only of genuine cases of tuberculous peritonitis, not of those which present numerous miliary nodules without further inflammatory changes of the peritoneum. For such cases offer even the experienced clinician many diagnostic difficulties . . .

I belive that the configuration of intestinal tympanites and its localization upon the abdominal walls often differs in both diseases discussed (carcinoma and tuberculosis of the peritoneum) from that usually seen with free ascites (non-inflammatory conditions) . . .

In all our cases of peritoneal carcinoma the mesentery had shrunk and in consequence the intestines were pulled up in a packet . . .

We know that the mesenteric root starts at the lumbar spine and proceeds obliquely from the second lumbar vertebra to the (right) sacroiliac symphysis. On the basis of these conditions it is self evident why the mass of loops of small intestine is displaced more to the right, especially in scirrhous carcinoma. In this disease the mesentery frequently shrinks considerably, subsequently the packet of small intestine must follow the shrunken fold and since this has its root on the right the small intestine must be found more in the right than in the left abdomen, provided such displacement is not prevented by special conditions . . .

* A sketch of the life of Thomayer will appear when this material is published in book form.

† Translated from the original German.

ZEITSCHRIFT

FÜR

KLINISCHE MEDICIN.

HERAUSGEGEBEN

VON

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IN WIEN.

Siebenter Band.

Mit 10 lithographirten Tafeln.

BERLIN 1884.
VERLAG VON AUGUST HIRSCHWALD.
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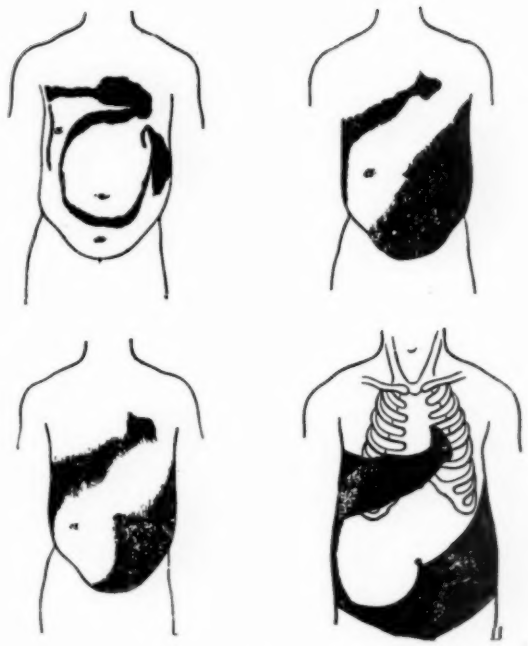
A



B

FIG. 119.

A. Facsimile of title page of journal in which original article by Thomayer appeared.
B. Figures reprinted from article.

Upper left. Typical non-inflammatory ascites.
Upper right. Malignant peritonitis secondary to carcinoma of ovary.
Lower left. Malignant peritonitis secondary to carcinoma of stomach.
Lower right. Tuberculous peritonitis.
Shaded area—area of percussion dullness.
Clear area—area of tympany upon percussion.
Note that with non-inflammatory ascites the area of tympany is central in location while the dullness (fluid) is peripheral, a concave line marking the union of tympany with dullness. (upper left.)
Note that with malignant and tuberculous peritonitis (inflammatory ascites) the tympany is found to the right side of the abdomen and along the line of the root of the mesentery while the dullness lies to the left, extending high in the left flank. (Upper right, lower left and right.)

XIX.

Beitrag zur Diagnose der tuberculösen und carcinomatösen Erkrankungen des Bauchfells.

Von

Doc. Dr. Josef Thomayer (Prag).

Die klinische Diagnose der tuberculösen und carcinomatösen Peritonitis wird von Manchen als schwierig, von Anderen dagegen als leicht dargestellt, ein Umstand, der offenbar davon abhängig ist, was für Fälle die Einen oder die Anderen zu untersuchen hatten. Denn es ist zweifellos, dass die Diagnose beider genannten Affectionen sehr leicht sein kann. Wenn sich z. B. bei einem Kranken, der an einem tastbaren Magencarcinom leidet, im Laufe dieser Affection in der Bauchhöhle deutliche secundäre Knoten entwickeln, wenn nebenbei die Bauchhöhle sich mit Flüssigkeitserguss zu füllen beginnt, so braucht der untersuchende Arzt gewiss keineswegs besonders scharfsinnig zu sein, um die richtige Diagnose zu stellen. Das Gleiche gilt von Fällen, in denen neben ausgesprochener Lungentuberculose unter heftigen Unterleibsschmerzen ein freier Ascites sich entwickelt, ohne dass eine Leber- oder Nieren- oder Herzerkrankung anzunehmen wäre.

Anders verhalten sich jedoch die Umstände, wenn wir einen Kranken zu behandeln haben, der zwar alle Erscheinungen von hochgradigem Ascites darbietet, bei dem jedoch sowohl local, als in den übrigen Organen und Geweben das Untersuchungsresultat negativ bleibt.

Denn tuberculöse Peritonitis kann sich bekanntermassen entwickeln neben isolirter Tuberculose der Mesenterialdrüsen, neben occulter Tuberculose des Urogenitalapparates [1]), neben unbedeutender Lungenaffection

and bedeutend entwickelter Darmtuberculose, kurz in einer ganzen Reihe von Fällen, in denen es sich zwar um eine im Ganzen typische Affection des Peritoneums handelt, ohne dass die Diagnose gar so leicht zu stellen wäre. Hierbei habe ich nur Fälle von wirklicher tuberculöser Peritonitis vor den Augen, und berücksichtige nicht solche, in denen zahllose miliare Knötchen ohne weitere entzündliche Veränderungen am Peritoneum vorgefunden werden. Denn solche Fälle bieten selbst dem erfahrensten Kliniker wohl manche diagnostische Schwierigkeiten.

5 Ich glaube nämlich, dass die Contouren des tympanitischen Darmschalles sowie auch ihre Localisation an den Bauchdecken bei beiden in Frage stehenden Affectionen mitunter eine andere ist als es bei freier Ascitesflüssigkeit gewöhnlich der Fall ist.

In allen unseren Fällen von 8
Carcinom des Peritoneums war das Mesenterium geschrumpft und die Gedärme in Folge dessen zu einem Knäuel zusammengeballt.

Wir wissen ja, dass 9
der Radix mesenterii an der Lendenwirbelsäule beginnt und in schiefer Richtung vom zweiten Lendenwirbel zur rechtseitigen Symphysis sacroiliaca verläuft. Auf Grund dieser Verhältnisse ist es von selbst einleuchtend, warum speciell bei skirrhösen Krebsformen der Dünndarmknäuel mehr nach der rechten Seite verschoben wird. Das Mesenterium schrumpft aber bei dieser Krankheitsform häufig in ausserordentlichem Maasse; in Folge dessen muss der Dünndarmknäuel dem schrumpfenden Gekröse folgen, und da dieses rechterseits seinen Ursprung hat, so muss auch dann der Dünndarm mehr in der rechten als in der linken Hälfte vorgefunden werden, vorausgesetzt dass ihn besondere Verhältnisse an einer derartigen Verschiebung nicht hindern.

Auf Grund dieser Verhältnisse ist es mir klar, dass unter solchen Umständen das Percussionsresultat ein wesentlich anderes ist, als bei gewöhnlichem freiem Ascites.

Die vorgehenden Auseinandersetzungen betreffen zwar nur das Carcinom des Bauchfells, doch gilt für die Tuberculose mutatis mutandis dasselbe. Denn auch bei der sogenannten tuberculösen Peritonitis kommen schrumpfende Processe sowohl im Omentum als im Mesenterium vor, wodurch dann die Dünndarmschlingen ein ähnliches Schicksal erfahren wie beim Carcinom. Deswegen sind auch die die Percussionsverhältnisse zur Anschauung bringenden Schemata einander sehr ähnlich und bei beiden Krankheiten analog. Möglicherweise geschieht die Schrumpfung des Gekröses bei Tuberculose nicht in so intensiver Weise wie beim Carcinom, die eben in den schematischen Zeichnungen der Darmschall nicht so rechterseits vorwiegt wie bei den Carcinomen, doch besitze ich hierüber keine Erfahrungen.

Es ist schwer bestimmbar, warum derartige Fälle nicht schon längst eine neue genauere Durcharbeitung der Percussionsverhältnisse bei Ascites veranlasst haben, doch scheint es, dass die Ursache in folgenden Umständen zu suchen ist. Ein Practiker wendet Percussion bei einem Ascites wohl zuletzt an, früher sucht er sich durch andere Untersuchungsmethoden den Aufschluss zu verschaffen und percutirt wohl zumeist, wenn er mit seiner Diagnose im Klaren ist. Denn auch in der Klinik werden in ähnlichen Fällen Palpation, chemische, mikroskopische Untersuchungen, Probepunctionen etc. viel mehr geübt, als die simple Percussion des Unterleibes, die wohl nur in Cursen für Anfänger genauere Berücksichtigung findet. Dasselbe geschieht auch in der Praxis, und es ist dies nur zu bedauern, weil die klassische physikalische Untersuchung leicht ist und überall angewendet werden kann.

Halten wir uns vor den Augen, dass das schrumpfende Gekröse den Dünndarmknäuel nach der rechten Seite zu ziehen die Tendenz hat, so werden wir in speciellen Fällen mit unserer Diagnose vorsichtig sein.

FIG. 119c. Facsimile of excerpts from original article by Thomayer.

These conditions make it plain that the result of percussion is essentially different from that found with ordinary free ascites . . .

These explanations concern carcinoma of the peritoneum yet they hold good also for tuberculosis. For even so-called tuberculous peritonitis presents shrinking of the omentum as well as the mesentery, which causes similar conditions for the loops of small intestines as in carcinoma. Therefore the diagrams illustrating percussion conditions are very similar and analogous in both conditions. Probably mesenteric shrinkage with tuberculosis is not as intensive as in carcinoma for the diagrams do not show that tympanites predominates as much on the right as in carcinoma, yet I have no observations on that fact . . .

It is rather difficult to understand why in such cases percussion conditions in ascites have not long ago caused more exact revision but probably the cause is the following: the practical physician tends to use percussion as the last resort in ascites and tries to base his diagnosis first on other methods of examination, using percussion only when in doubt about diagnosis. In the clinic also in similar cases palpation, chemical and microscopic tests, exploratory puncture, etc. are used rather than simple percussion of the abdomen which is used only in courses for beginners. The same thing happens in practice and it is much to be regretted for the classicial physical examination is easy and is applicable in every case . . .

If we remember that the shrinking mesentery tends to displace the mass of small intestines toward the right we shall be more careful in diagnosing individual cases . . .

QUESTIONNAIRE

1. Describe the development of the peritoneal cavity.
2. From what germ layer does peritoneum arise?
3. What is the splanchnic mesoderm; the somatic mesoderm; endothelium?
4. Give derivation of the words splanchnic, somatic.
5. What is the primitive dorsal mesentery; its relation to the mesenteries omenta and peritoneal folds in the adult?
6. Describe the attachments between liver and stomach; between stomach and colon; between liver and anterior abdominal wall.
7. Why are the falciform ligament and lesser omentum at right angles to one another?
8. Explain why some portions of the gastrointestinal tube are firmly adherent to the parieties while others are freely movable?
9. Explain how the jejunum and ileum become attached to the posterior abdominal wall by a six inch mesentery?
10. How does the superior mesenteric artery come to cross the terminal portion of the duodenum?
11. Why does the root of the transverse mesocolon overlie the duodenum rather than is attached directly to the abdominal wall?
12. Give some differences in appearance between a sarcomatous ulcer and a carcinomatous ulcer?
13. Give a clinical differentiation between a desmoid and an epithelioma of the abdominal wall.
14. Which are more common within the abdomen, benign or malignant newgrowths?
15. What is the relative frequency of primary and of secondary neoplasms within the peritoneal membrane?
16. State most common sites from which secondary malignant peritoneal newgrowths arise.
17. From what retroperitoneal tissues do newgrowths arise?

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18. How may retroperitoneal newgrowths be differentiated from those arising from peritoneum?
19. From what cells do primary malignancies of peritoneum originate?
20. Discuss some of the names given to primary newgrowths of peritoneum.
21. Describe the gross pathology of primary peritoneal malignancies.
22. What conditions do these newgrowths simulate? Give differential diagnosis.
23. What are the most common causes of bloody peritoneal fluid?
24. Discuss the prognosis and treatment for primary peritoneal malignancies.
25. Give a list of intra-abdominal tissues arising from the three embryonic germinal layers.
26. What part does each germ layer play in the formation of bowel, liver, spleen, pancreas?
27. What are chromaffin bodies? What is their histogenesis?
28. State the similarities between chromaffin system and sympathetic nervous system.
29. In what ways does a knowledge of the germinal origin of tissues aid the clinician?
30. Why should the practical surgeon review the germinal origins of the tissues with which he deals?
31. Why is the left vagus distributed to the anterior wall of the stomach?
32. Describe the embryonic rotation of the stomach.
33. What are the anatomical divisions of the duodenum? Describe each.
34. Describe the relation of the root of the transverse mesocolon to the duodenum.
35. What is the most frequent site for duodenal ulcers?
36. What is the value of roentgen-ray examination for peptic ulcer?
37. Why is it correct to refer to a duodenal ulcer as a variety of peptic ulcer?
38. What is the duodenal cap? Describe in detail.
39. What are the roentgen-ray findings with duodenal ulcer?
40. Discuss the limitations of roentgen ray as a diagnostic aid in determining the presence of active peptic ulcers.
41. Do healed duodenal ulcers cause evidence of deformity of the duodenal cap?
42. What is the duodenojejunal angle? How produced?
43. Describe methods for locating the proximal jejunum.
44. What three peritoneal reflexions meet at the duodenojejunal junction?
45. Describe the location of the duodenojejunal junction.
46. Why does the proximal jejunum abruptly enter the abdomen from below the root of the transverse mesocolon?
47. What is the ligament of Treitz?
48. Describe the embryonic rotation of the intestines.
49. What is the duodenocolic isthmus?
50. What is meant by saying that intestinal rotation occurs upon the superior mesenteric artery as an axis?
51. Does the artery itself rotate during intestinal rotation?
52. Describe the effect upon the branches of the superior mesenteric artery of intestinal rotation.
53. Why does the appendix at one period of development come to be lodged below the liver?
54. What is meant by the embryonic position of the appendix?
55. Describe methods for studying the phenomenon of intestinal rotation by means of models.
56. What is meant by saying that the gastrointestinal tract always remains basically a midline structure?
57. What is meant by raw or uncovered areas of the abdomen?

58. What portions of colon are partially retroperitoneal and which are supplied by mesocolons? Explain these arrangements.
59. To what height is the right colic flexure fixed; the left colic flexure?
60. What is the omental bursa?
61. What is the relation of the transverse mesocolon to the omental bursa?
62. In what percentage of individuals may an ascending or descending mesocolon be expected?
63. Describe the mobilization of the cecum and ascending colon.
64. Describe the root of the mesentery as to length and position.
65. Describe the structure of the mesentery.
66. What is the relation between superior mesenteric artery and mesentery?
67. Map out the mesentery on the anterior abdominal wall.
68. What are the three intestinal topographical zones?
69. Describe methods for studying the mesentery.
70. How may the bowel be drained of its toxic contents during operations for acute intestinal obstructions?
71. What structures are found between the peritoneal layers of the mesentery?
72. Describe the attachments of the duodenum.
73. What is the hepatoduodenal ligament; the duodenocolic ligament?
74. When is it advisable to mobilize duodenum?
75. Describe a method for mobilization of the duodenum.

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